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DEVELOPMENTAL PATHOLOGY: A NEW FIELD IN MEDICINE*†

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IN RECENT years, a new and thrilling discipline of biology and medicine has grown out of research in various fields, almost unnoticed by the medical profession: this is developmental pathology. Much fragmentary knowledge had accumulated for many years, but it has only recently been possible to integrate and understand most of it. Since the developmental processes occurring in embryonic life are more numerous and fundamental than those of later periods, developmental pathology is largely concerned with the embryo. Yet, it is obvious that some measure of development goes on and may go wrong after birth, and disturbances of postnatal life do not differ essentially from prenatal ones, as will be discussed later. Clearly separated from these abnormalities resulting in malformations are, in the minds of many pathologists, the diseases of postnatal life, as for instance those caused by infection or poisoning. However, these diseases are no more limited to postnatal life than are developmental aberrations to the embryonic period. Autopsies in stillborn and newborn infants reveal an unexpectedly high incidence of necrosis, inflammation, or fibrosis in various organs, indicating the occurrence of typical disease processes in the embryo.

The relationship of malformation and disease (if such subdivision is at all permissible) is not limited to their occurrence during the same periods of life. More fundamental relations of a causal nature are known to exist in many instances. It is obvious that many malformations that are not outright lethal produce disease. As examples, the congenital interruption of bile ducts with

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consequent cirrhosis and insufficiency of the liver, or certain malformations of the heart leading to circulatory embarrassment may be mentioned. On the other hand, we have learned not so long ago that rubella during the first trimester of pregnancy causes malformations of the brain, eyes, inner ears, heart, and other organs.[1] A condition which cannot be definitely classified as either malformation or disease is mucoviscidosis[2] with its best known manifestation, cystic fibrosis of the pancreas. In this condition, the prenatal disturbances in the structure of various glands and ducts might be considered as malformations. Yet, there are indications that these changes are due to abnormal function of these glands, probably on a genetic basis,[2, 3, 4] or to fetal inflammation[5]; in other words, disease. Finally, there are genetically determined degenerative changes, the products of which are classified as malformations when they appear in early life (for instance, taillessness in mice), and as diseases when they occur late (for instance, various degenerative diseases of the nervous system). It follows from these considerations that there is no inherent difference between malformations and disease, and that all classifications, recognizing these two distinct categories, are of necessity arbitrary.

A few illustrative examples will be cited in order to demonstrate the extent of existing knowledge in developmental pathology and its usefulness to the pathologist and practicing physician. Obviously, much of the systematic and well-controlled work has been done on animals, and some of this will be mentioned because of its general significance. For more detail the reader is referred to a review which appeared elsewhere.[6]

Hereditary abnormalities in man are recognized in increasing numbers, and the rapidly expanding knowledge in this field[7] has proved useful in many cases in which eugenic advice was desired. In animals, hereditary traits afford a unique opportunity to study the biology of abnormal development in great detail because various stages of these abnormalities are readily available for description and experimentation. It should be remembered that the inheritance of abnormal traits is governed by the same laws as is the heredity of normal properties. Inherited abnormalities are reproduced just as faithfully as normal traits, and these inherited abnormalities are susceptible to modification by the influence of environment just as normal traits are. Snyder[8] has compiled in concise form the reasons why the expression of hereditary traits may vary among individuals who carry the genes responsible for these traits. The differences in expression are accounted for not only by the action of other genes which may increase or reduce the expression of a particular trait, but also by the action of environmental factors. These points may be illustrated by work done on some of the very well-studied hereditary abnormalities in chicks. Landauer[9] has bred chicks with a hereditary trait producing an abnormally short upper beak. In using those birds which showed the least effect, he was able to select his animals for the presence of modifying factors to such an extent that finally the expresssion of the gene for short upper beak was entirely inhibited in the great majority of birds. The following is an example of the action of environment upon the expression of hereditary malformations.

Polydactylism in the chick can be prevented in a large number of cases by reducing the incubation temperature at a certain specific time of embryonic development (Sturkie[10]). The embryo will then develop normal extremities.

In mammals, there are also indications of the existence of genetic and environmental modifiers. This has been demonstrated particularly in taillessness of mice[11] and rats.[12]

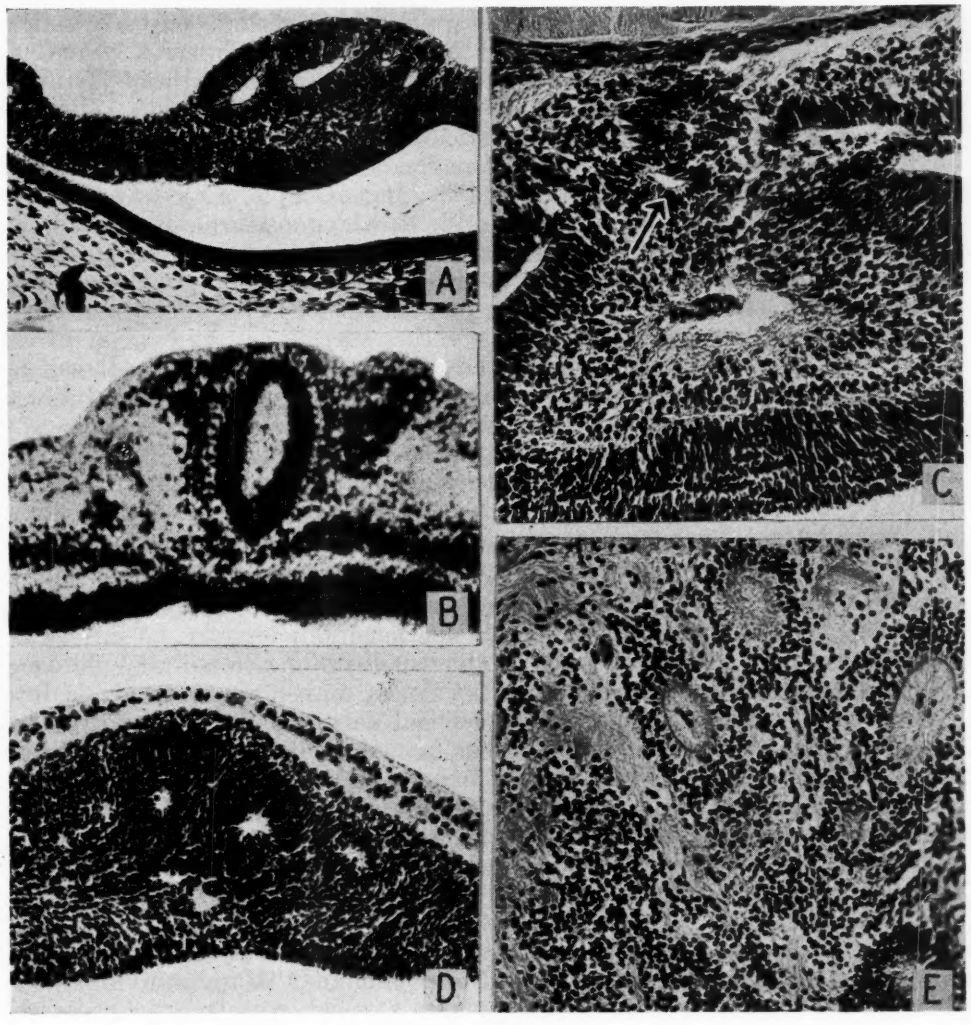

Fig. 1.—An example of similar abnormalities produced by various agents: rosettes in the retina. *A*, A hereditary abnormality in the chick. *B*, Retina of a human fetus after irradiation with x-rays (from Goldstein and Wexler,[15] courtesy of authors and American Medical Association). *C*, Rosettes in a vitamin A deficient rat embryo (specimen courtesy Dr. J. Warkany). *D*, Retina of a rat, one week after puncture of the eyeball at birth. *E*, Retina of an infant with microphthalmia.

The uterine environment of the mammalian and presumably of the human embryos is not invariably favorable. It has been shown that when embryos of mice which are homozygous for a lethal trait known as *yellow*, develop in the uterus of a normal mouse, they survive for a longer time than they would in the uterus of a *yellow* mouse.[13] This work was done by transplanting ovaries of *yellow* mice to others which do not carry that factor. Another investigation[14] in mice showed that the litter size depended on the uterine environment. In other words, the mortality among very early embryos is apparently dependent, at least in part on the uterine environment.

Just how an abnormal genetic trait produces abnormalities during development is not known. It has been suggested by many investigators that a temporary inhibition of development may cause abnormalities and that this inhibition will particularly affect certain areas which are highly susceptible at the given moment. The great susceptibility of certain parts is believed to be due to their particularly active growth and development. Similarly, environmental influences are assumed to affect most severely those portions of the embryo growing most rapidly at the moment of their action. It is only reasonable to assume that one might simulate the effect of genetic abnormalities by environmental influence, and this has actually been done, resulting in so-called phenocopies[15] of hereditary traits. For example, a recessive trait was found in chicks which, when present in the homozygous form, produces microphthalmia and finally leads to death of the chick about the time of hatching. In the development of the eyes, the first discernible abnormality consists of formation of so-called rosettes in the retina.[16] These rosettes are very small cavities in the solid tissue of the retina surrounded by a layer of cells which resembles the future layer of rods and cones (Fig. 1, *A*). It has been found that treatment of various normal embryos with x-rays[17, 18] results in the formation of similar rosettes (Fig. 1, *B*), and also in the development of microphthalmia. Other procedures such as avitaminosis A[19] (Fig. 1, *C*), or mechanical injury[20] (Fig. 1, *D*) which tends to reduce the size of the eyeball will also produce rosettes very much like the hereditary ones. Similar formations occur in spontaneous malformations of the eyes in man (Fig. 1, *E*).

In dealing with hereditary abnormalities, one must remember that the abnormal genotype of a given individual remains the same throughout life and that it cannot be altered at will by any experimental procedure. That explains the great tenacity with which certain abnormalities of a hereditary nature express themselves throughout life. A clinically important example is intersexuality. In some individuals, an abnormal determination of sex results in the development of various combinations of male and female structural traits in the genital organs. These combinations are so numerous and unpredictable that even the inspection of the internal genitals does not permit the physician to determine whether the individual is a male or female. The reason for this is obvious: the individual is neither male nor female. It has developed in perfect accordance with its own genotype which has determined that it will be an intersex. Since in every individual, normal or abnormal, the genetic sex has a great tenacity, it is impossible to establish in an intersex a normal male or female sex by any procedure at our command. Many individuals have been observed who showed external genitals which were more female than male in appearance. They had inguinal hernias, and when they were explored by a surgeon, testicles were found in them. It was reasoned that these testes interfered with the normal female development of the individual and the gonads were therefore removed. The effect was comparable to menopause, but none of these individuals became any more female by removal of testes than they had been before. It has therefore been suggested by biologically well-informed workers[21, 22] to abstain from removing the gonads of these individuals and limit oneself to such plastic and purely external interference as will make the life of the individuals more nearly normal. Another important point in this connection is that no diagnostic procedure, including biopsy of the gonad, will permit one to determine in an intersexual infant or child whether it eventually will have male or female feelings. This is another reason for interfering as little as possible with the genitals of these persons, particularly as long as their psychic sex has not adequately manifested itself.

Contrast with this the conditions in those intersexes who have a normal male or female genotype. These cases have developed abnormally because they have been subjected to hormonal influences which interfered with the normal manifestation of their genetic sex. The most common cause is a tumor of the adrenal cortex which may, at any time before or after birth, tend to reverse the sex of its bearer.[23] In this case, a normal genotype is present and, if one is successful in removing the cause of the disturbance, the organism will attempt by itself to revert to its normal sex.

The great permanent power of the genetic sex is also well illustrated by the following experiment in chicks. It is easy to transform male chick embryos completely into females by the injection of estrogen into the egg. If this is properly done, a male may be transformed to such an extent that morphological examination will not reveal its true genetic sex at the time of hatching. Yet, if these animals are allowed to live without any further hormonal treatment, they will eventually tend to revert to their original male sex.[24, 25] This happens despite the fact that at birth these chicks have ovaries which might be expected to produce sufficient female hormones to assure female development for the rest of their lives. Actually, the power of the hormones of the gonads during early periods of development has been greatly overrated. Recent investigators have concluded from many lines of evidence that male or female development of the so-called secondary sex characters in the embryo is not at all dependent on a secretion of the embryonic gonads. The gonads may be removed and the embryos will develop normal male or female traits in their absence.[26]

One of the most intriguing features of hereditary malformations is the appearance of complex syndromes which affect various organs or organ systems in a manner that cannot be explained by a common basis in their development. In some instances, detailed studies will reveal a common basis such as in the case of a hereditary abnormality in the rat which has been described by Grüneberg.[27] These rats show various skeletal abnormalities and die of pulmonary infections. A basic abnormality in the development of their cartilaginous skeleton was found, which accounts not only for the deformities of their bones but also for such changes in the ribs and in the cartilages of the respiratory passages that emphysema and pulmonary infection terminate their lives. Another instance might be mentioned in which the common basis for a great variety of abnormalities was found. A strain of mice was discovered which showed various abnormalities of the extremities, jaws, and eyes. Investigation of the embryonic development[28] revealed that collections of cerebrospinal fluid escape from the brain and travel as blebs under the epidermis of the embryo. The blebs keep moving until they are trapped at some point. They do permanent damage only at those points from which they can no longer escape, such as the feet and jaws as well as the region of the eyes. When the fully developed malformations are seen, the blebs have long disappeared and no one could determine the mechanism of origin from the study of the fully developed condition alone.

In other instances, various manifestations of an abnormal genetic trait appear at a stage which we cannot apprehend with our morphological methods. As a result, a variety of seemingly unrelated changes are present at the earliest stages at which we can determine abnormalities in the development of these individuals; this is the case in the *Creeper* chick. Hamburger[29] has compiled our present knowledge of this abnormal trait and has shown that four different abnormalities appear in the homozygous *Creeper* embryo and cause the defects of blood vessels, skeleton, and eyes.

One mechanism of the development of hereditary abnormalities must be mentioned in more detail because it also occurs in postnatal periods. This is the degeneration of previously normal-appearing parts. We know that during postnatal life a great variety of degenerative hereditary diseases of the nervous system, the muscles, and other parts of the body appear and the morphological sequence of stages has been studied in considerable detail in several instances. Retinitis pigmentosa is a well-known example, thoroughly investigated from the genetic and morphologic points of view.[30] Old-age changes may have a similar genetic background. Gorer[31] found that three inbred strains of mice develop distinctly different changes in the kidneys, in a high proportion of cases, as they grow old. One shows hyperplasia of Bowman's capsules; the second strain develops necrotic lesions in the papillae, and cysts in the cortex; and in the third one there is hyaline degeneration of the connective tissue stroma.

During the past few years it has been found that processes similar to these heredodegenerative changes may occur in the early embryo and account for conditions which anyone would consider as malformations. There are several hereditary traits which determine the absence or reduction of the tail in mice[32] as well as in chicks.[33, 34] Some of these have been studied embryologically and it was found in every case that the primordium of the tail is at first present as in any normal embryo and then, at a given stage which is strictly characteristic for each of these hereditary traits, degeneration sets in, the tissue becomes necrotic, and finally sloughs off. In another instance involving defects of the feet and ears in rabbits, hemorrhage and necrosis occur, beginning on the sixteenth day of gestation, and result in the loss of previously well-developed parts of the body.[35] These examples illustrate best the fallacy of the method of the old teratologists who sought to establish the manner of development of a malformation by studying only the fully developed abnormality and determining the presumptive stages in embryonic life in which the particular organ failed to undergo its normal development. None of these speculations took into account the possibility of secondary degeneration of a previously normal primordium. In this connection, it is interesting to note that, in mice as well as in rats, there is a hereditary condition of rodless retina. In mice, the rodless retina is due to a failure of differentiation.[36] In rats, however, the retina is at first normally developed and then undergoes secondary degeneration after birth.[37]

Most of the mutations which produce hereditary abnormalities arise spontaneously. There are but a few examples in which mutations have been produced in higher animals, e.g., by treatment with x-rays. It is generally acknowledged that the chances of producing such mutations in man are very low;[38, 39] yet, with the increased use of biologically highly active methods in medicine it becomes important that we realize the possibility of danger to the genetic mechanism which may manifest itself in the progeny of the treated person. This should be remembered particularly when x-rays, or such substances as nitrogen mustard, are used in a manner in which they may affect the germ cells in the gonads without completely destroying their activity. It is also important to distinguish these effects on germ cells from those upon the developing embryo which do not affect the genotype; the latter will be briefly mentioned below.

Developmental abnormalities caused by influences of the environment are of relatively little importance in the mammalian embryo. The uterine environment protects the embryo very well although this protection is not as complete as one might believe at first glance. We have already mentioned that the uterine environment in itself is not uniformly favorable and may have an effect upon the development of the embryo.

Most of the physical and chemical agents which may influence development have been studied in animals other than mammals. Some of this work should be briefly mentioned in view of its significance for the understanding of the mechanisms of abnormal development in general. It is obvious that mechanical influence destroying or removing parts of the embryo may result in deformity. There is no need for elaborating on this subject. Work with chemicals, however, is of great interest. Long ago, Werber[40] produced very severe malformations in fish embryos by organic substances, for instance, acetone, which may also occur in the human organism. These malformations may assume bizarre forms and in some cases isolated eyes have been found growing on the surface of the yolk. Werber's[41] suggestion, that in man malformations may be due to the same cause, is very improbable because sufficient concentrations of acetone can hardly be assumed to be compatible with pregnancy in the human species. Much work of general interest has been done in amphibians with lithium salts and in chicks with selenium compounds. A recent investigation of Gillette and Bodenstein[42] in newts has served to confirm the above-mentioned hypothesis that rapidly growing tissues are particularly sensitive to damaging agents. These authors treated newt embryos with one of the nitrogen mustards and found that rapidly dividing cells are selectively affected. It could even be shown that among tissues of the same histologic type those portions which grow rapidly are severely damaged, whereas others, which are quiescent, escape injury.

The effect of various deficiencies has been studied in the embryos of mammals. Warkany and his co-workers[43] studied the effect of riboflavin deficiency upon rat embryos and found that various skeletal abnormalities as well as cleft palate may result. The production of eye malformations in rats by maternal vitamin A deficiency has also been investigated.[43] Reports of human cases of fetal rickets and scurvy are inconclusive, but there can be no doubt that vitamin deficiencies may have an effect upon the human fetus.

Oxygen deficiency may affect the older embryo whenever oxygenation of the mother's blood or circulation of the embryo's own blood is impeded. It occurs most frequently during labor, and at that time some degree of it is normal and well tolerated. However, excessive anoxia may result in damage to the brain, lungs, and possibly other organs. Brain damage and its pathological and functional manifestations have been described in human newborns by Schreiber[44] and others, and in experiments with newborn guinea pigs by Windle and co-workers.[45] Histologically, necrosis and hemorrhage are found. The lungs may suffer by the aspiration of vernix and meconium when anoxia stimulates strong respiratory efforts in utero. While some lungs appear to tolerate moderate amounts of these materials fairly well, others will be unable to expand when the bronchioles are lined with thick, fatty vernix,[46] and still others will become the seat of pneumonia shortly after birth.[47] In young embryos of lower animals, severe malformations can be produced by anoxia; this is not known to occur in man.

It is common knowledge that irradiation with x-rays may severely damage the fetus, and result in malformations of various organs.[48] Similar results have been obtained experimentally in mammals.[49] It has been established that irradiation at different periods of embryonic development results in different and fairly well-defined types of malformations.

In malformations, just as in normally developing organs, the development of one part often depends on that of an adjacent part. On the one hand, this insures proper relations of the parts concerned; on the other hand, abnormalities in development may extend far beyond the original limits of the

damage by similar mechanisms of dependent development. The following example concerning the urogenital tract will serve to illustrate this point. In the normal embryo, the mesonephros as well as the permanent kidney and the uterus depend for their normal development on a normal Wolffian duct. If during development the growing end of the Wolffian duct is damaged in a minute area, not only the entire duct fails to develop from that point on, but the other organs which depend on it for their development will also be absent (Fig. 2, *A*). The result is a complex of abnormalities which can be produced in chick embryos by destroying the growing end of the Wolffian duct (Fig. 2, *B*) and which also occurs relatively commonly in man and mammals as a spontaneous malformation.[50] This syndrome comprises after completed development, in the male, the absence of all or part of the epididymis, the ductus deferens, the kidney and ureter; and, in the female, all or part of the epoophoron, the tube, one-half of the uterus, and again the kidney and ureter (Fig. 2, *C*). All these organs can thus be damaged indirectly by destroying a minute group of cells at the growing end of the Wolffian duct in the early embryo.

Other correlations between developing organs are mediated by hormones. These substances play an important role in directing the development of various parts of the body before and after birth. Examples of endocrine disturbances are so well known that they need not be quoted here.

There are correlations between the nervous system and the organs supplied by it. These are of much greater importance after birth than they are in the embryo. Yet, even during prenatal development such influences are known to exist. Development of extremities will be inhibited to some degree when they are not properly innervated[51] and, in turn, development of certain portions of the spinal cord will be altered if the organs normally supplied by that portion develop abnormally.[52, 53]

Finally, we come to so-called diseases of the fetus, that is, conditions which are comparable to diseases of postnatal life. The mere existence of these conditions shows that the protection of the human embryo is not fully dependable and that it is worth while to direct one's attention toward supervising the environment of the developing fetus in utero. One group, namely, vitamin deficiencies, has been briefly mentioned above. Another one concerns inflammatory processes. The problem of fetal inflammation and its relation to malformations has received extensive consideration in the field of pathology of the heart. We know that in certain congenital abnormalities of the heart conditions prevail which closely resemble the scarring after postnatal inflammation, for instance, rheumatic heart disease. There has been much argument as to whether those fetal conditions are, or are not, the outcome of fetal inflammation. It is quite possible that, as some authors assume, the existence of a thick layer of fibrous tissue under the endocardium (Fig. 3, *A, B*) is a developmental aberration rather than the result of inflammation.[54, 55] On the other hand, many observers have studied cases in which there was a diffuse scarring that involved all layers of the wall of the heart combined with areas of calcification and of inflammatory cellular infiltration. It is difficult to escape the conclusion that in these cases the findings are the result of a fetal inflammation.[56]

Much publicity has been given to the observation that a disease which was generally believed to be harmless can produce severe malformations of the fetus when it occurs during the first trimester of pregnancy. This is the case in rubella and occasionally in other virus diseases.[1] There is no agreement as to the percentage of cases in which malformations result, but the number of cases is certainly sufficiently large to warrant careful consideration and, if possible, prevention. The organs most prominently affected by ab-

normalities are the brain, eyes, and heart. Other organs, such as the inner ear and the teeth have also been found to be defective. Only a very small number of these cases have been examined at autopsy. The changes are not very conspicuous. In the eyes, a characteristic form of cataract which is believed not to occur in any other condition has been described by Swan.[57] The changes in the brain have, to the best of my knowledge, not been thoroughly investigated.

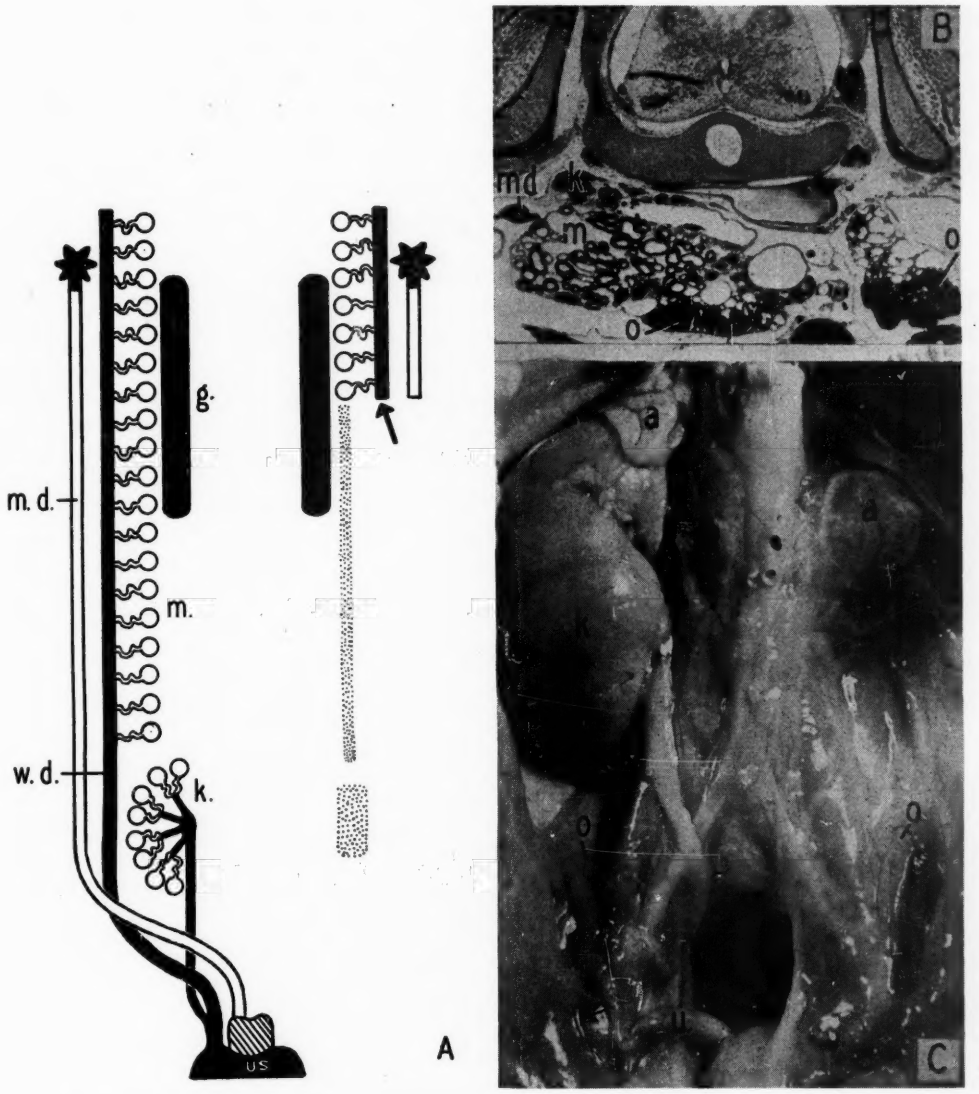

Fig. 2.—One primary abnormality causing a syndrome of malformations by dependent development. The diagram (A) shows on the left side the urogenital organs of the embryo developing normally. The parts which develop independent of others are shown solid black; those which depend on these parts are outlined. The right side of the diagram shows the multiple effects of termination of growth of the Wolffian duct at the arrow. All other defects are sequelae of this event. This can be done experimentally in chick embryos by destruction of the growing end of the duct. The result is shown in Fig. 2, *B*. The corresponding human malformation in a female infant is shown in Fig. 2, *C*. *a*, adrenal; *g*, gonad (ovary or testis); *k*, kidney; m, mesonephros; *m d*, Müllerian duct; *o*, ovary; *t*, tube; *u*, uterus; *u s*, urogenital sinus; *w d*, Wolffian duct.

In the heart, patent ductus arteriosus is the most common finding. The so-called fetal endocarditis or myocarditis which was mentioned above, is not found in this condition. We have no knowledge whatever of the mechanism by which the embryo is damaged if the mother acquires rubella during the first trimester of pregnancy. We do not know whether the disease affects the embryo directly, or just its environment, which may secondarily have its effect upon the developing organs of the embryo.

Another infection which appears to be entirely asymptomatic in most adults but causes severe disease in the fetus is toxoplasmosis. In contrast to rubella, toxoplasmosis is known to affect the fetus directly and the organism, a protozoan, has repeatedly been found in fetal tissues, surrounded by areas of tissue destruction and inflammation. Many organs may be affected, among them the brain, eyes, and heart.[58, 59]

Other instances of fetal diseases manifesting inflammation, necrosis, and fibrosis may be found in surprisingly many cases if one studies stillborn and newborn infants carefully at autopsy. In more than 10 per cent of all stillborn infants and newborn infants less than three days of age, one finds indications of a disease which must have occurred before birth.

The following is a selection of examples from the material gathered during two years at Kings County Hospital, and more recently in a survey of neonatal pathology to which many hospitals in Brooklyn have been contributing their material. Cases of fetal syphilis were not common and some of the manifestations described in all textbooks were not seen. However, two unusual cases were examined, which showed severe changes in the heart and intestine.

Several examples of the so-called fetal endocarditis were found (Fig. 3, *A, B*), and in some of them the microscopic findings strongly suggested that disease processes rather than primary developmental abnormalities had caused the changes.

In a two-month-old infant there were severe calcification and proliferation in the wall of the coronary arteries and almost all other arteries of large and medium size which could be examined (Fig. 3, *C*). The findings closely resemble those in other cases reported in the literature, and in addition very early stages of the abnormality were seen in the media of the aorta.

Focal necrosis in the media and adventitia of coronary arteries (Fig. 3,*D*) was found at first in two newborns, and when sections from other infants were re-examined, the number of cases rose to eighteen. The cause and the significance of these lesions are unknown.

The liver appears to be the seat of pathologic changes in many instances. Extensive necrosis of liver tissue (Fig. 4, *A*) was found in several stillborn and newborn infants. Two infants aged two and three days, respectively, died with cirrhosis of the liver, without evidence of obstruction of bile ducts (Fig. 4, *B*). An infarct-like area of necrosis with proliferation of granulation tissue at its borders (Fig. 4, *C*) was present in the liver of a 10-day-old infant and in several instances there were foci of replacement of liver tissue by connective tissue.

The pancreas of two stillborn infants showed acute inflammation with extensive infiltration by polymorphonuclear leucocytes (Fig. 4, *D*). In a number of other cases a large area of the pancreas was infiltrated, and the glandular tissue largely replaced by lymphoid tissue.

In one very premature infant measuring 28 cm. the peritoneal cavity was completely obliterated by fibrous adhesions. A small umbilical hernia was present. Indications of acute and chronic inflammation were seen in many

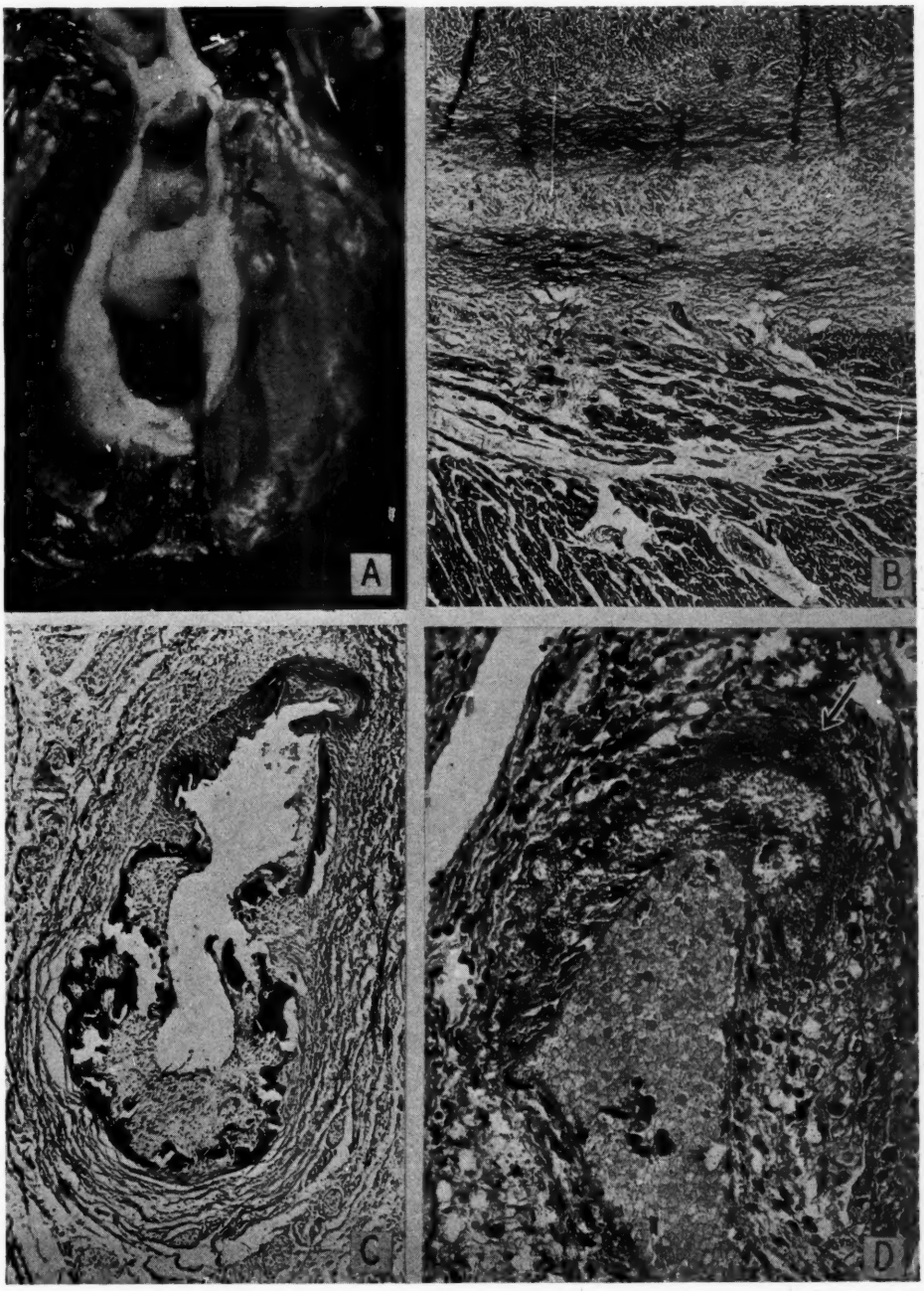

Fig. 3.—Fetal pathology of the heart. *A*, So-called fetal endomyocarditis, showing fibrous thickening of the endocardium of the left ventricle, and of the valves: *B*, A section of the same heart, with the thickened endocardium in the upper portion of the field, and part of the myocardium below. *C*, Calcification and intima proliferation in a coronary artery of a 2-month-old infant. *D*, necrosis in the media of a coronary artery in a stillborn infant.

parts of the body. They included, among others, the presence of numerous lymph follicles in abnormal locations.

It is extremely difficult to interpret most of these conditions because intrauterine life protects the embryo not only to some extent from damage, but also from examination by the physician. Information about the previous history

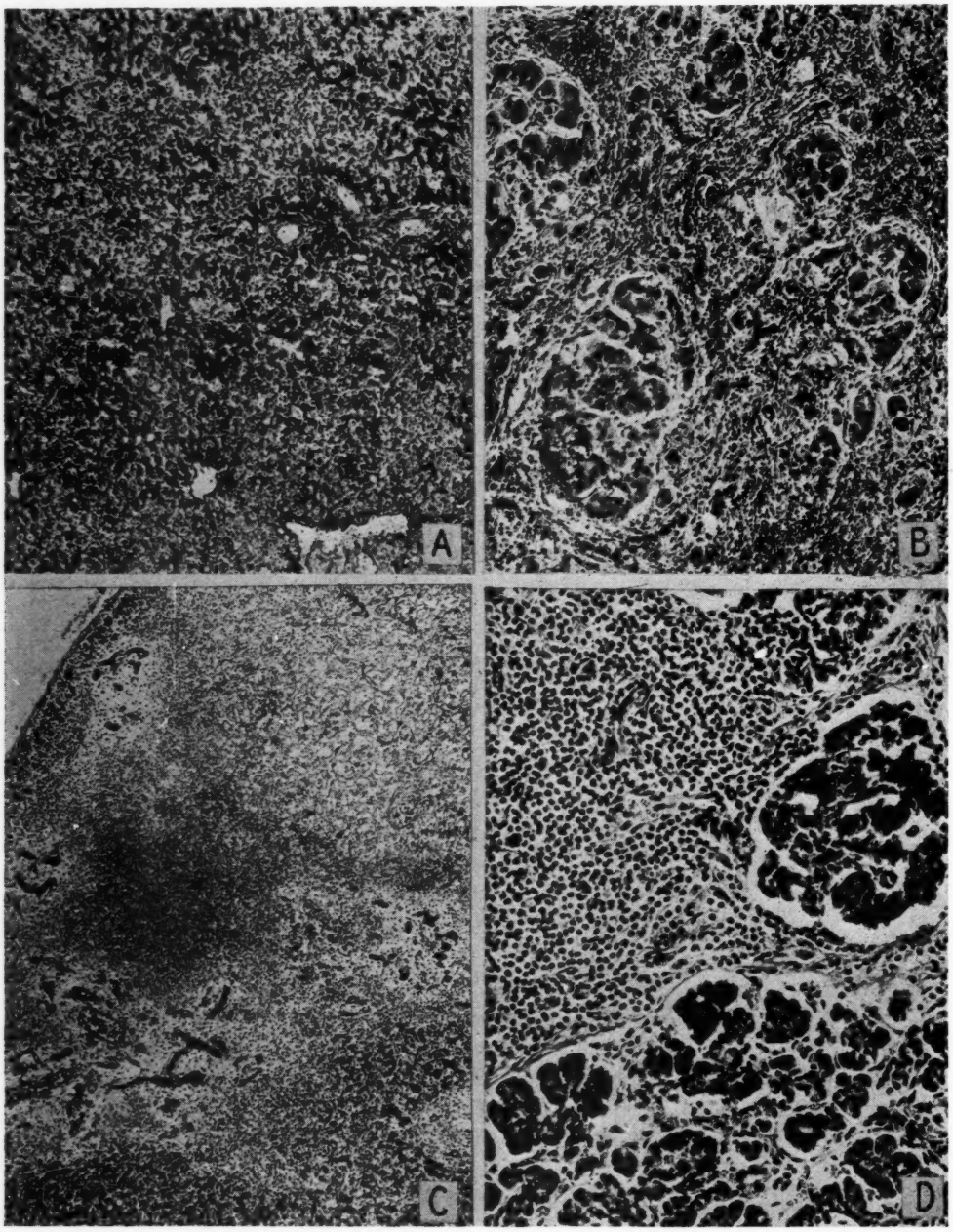

Fig. 4.—Fetal pathology of the liver and pancreas. *A*, One of many areas of necrosis in the liver of a 1-day-old infant. *B*, Advanced cirrhosis of the liver in a 3-day-old infant. *C*, Healing stage of an area of necrosis in the liver of an 8-day-old infant. *D*, Acute pancreatitis in a stillborn infant.

of these cases is, therefore, usually inadequate. In spite of this handicap, considerable advances have recently been made. This is true particularly with regard to the causes of several types of abnormalities which arise before or at birth, and affect the brain and the sense organs. A summary of recent and older information,[60] which also contains references to the pertinent literature, includes the following causes of mental deficiency, blindness, and deaf-mutism:

CAUSE		MENTAL DEFICIENCY	BLINDNESS	DEAF-MUTISM
Genetic.—				
Mutations		+	+	+
Heterospecific pregnancy		+	-	-
Environmental, Prenatal.—				
Infection:	Syphilis	+	+	+
	Toxoplasmosis	+	+	-
	Rubella	+	+	+
Deficiency:	Cretinism	+	(+)	+
	Mongolism	+	(+)	-
	Anoxia	+	-	-
	Vitamin A	-	+*	-
Paranatal.—				
Mechanical birth injury		+	-	-
Anoxia at birth		+	-	-

*Only in animal experiments.

The fact that we have learned so much during recent years about the mechanisms underlying abnormal development and that we have discovered the causes of several common developmental abnormalities in man shows that developmental pathology is now a field of practical significance to the physician. Not many years ago prenatal abnormalities were only the subject of doctors' theses and insignificant case reports. Today, our knowledge of these conditions has helped save many lives, and basic information now at our command should assure us of great advances in prevention and therapy in the near future.

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X-RAY VISUALIZATION OF THE PLACENTA: EXPERIENCES WITH SOFT-TISSUE AND CYSTOGRAPHIC TECHNIQUES IN THE DIAGNOSIS OF PLACENTA PREVIA

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IT IS an established fact that the placenta can be visualized in soft-tissue x-ray films in over 90 per cent of all women who are in the third trimester of pregnancy. This was forecast by Speidel and Turner[1] in 1924. In a paper dealing chiefly with x-ray visualization of the uterus and adnexa with the aid of artificial pneumoperitoneum, they stated: "It should be possible, by means of the roentgenogram, by the relation that the head of the fetus bears to the lower segment of the uterus, to determine the degree of encroachment of the placenta upon the internal os, and whether we have a central, lateral, or marginal placenta previa."

During the past several years at the Boston Lying-in Hospital we have made x-ray studies of all cases of uterine bleeding and of transverse or oblique position of the fetus occurring during the third trimester of pregnancy. The purpose of this paper is to report our experience regarding the x-ray diagnosis of placenta previa through the use of the soft-tissue technique introduced by Snow and Powell[2] and the cystographic method first described by Ude, Weum, and Urner.[3]

Historical

There has long been interest in the determination of the position of the placenta in the uterus. In 1898, Holzapfel,[4] working at the Frauenklinik at Erlangen, studied 107 placentas with their attached membranes, using a flotation and sac distention method in a tank of water. He found that 39.2 per cent of the placentas had been located chiefly on the anterior wall of the uterine cavity, 42 per cent had been on the posterior wall, 13 per cent had been implanted principally in the region of one or the other Fallopian tube openings, 4.7 per cent had been on one of the lateral walls, and in one case, or 0.93 per cent, the placenta had chiefly occupied the lower uterine segment. Torpin,[5] using the same technique, more or less duplicated these findings in 1938.

The first presented case we could find in the world literature in which the human placenta, in situ in its natural state, was visualized in an x-ray film without the use of radiopaque media is that reported by Baumann[6] in 1930. In a general paper on roentgenologic diagnosis during pregnancy and labor, he included a reproduction of an x-ray which showed the fetus to lie in transverse position with no fetal parts in the lower uterine segment. He stated that the placenta was visible on the film itself, but the reproduction is poor and does not actually appear to show it. He made no reference to this case in the paper itself, merely referring to it in the caption under the picture as follows: "Transverse presentation as a consequence of placenta previa centralis. Placenta visible on the film. Cesarean section done."

Great stimulus was given to the study of x-ray visualization of the placenta later in 1930, however, by the appearance of a paper by Menees, Miller and Holly.[7] They introduced a technique which they termed "amniography." This consisted of the addition of a denser contrast medium to the amniotic fluid in order to increase the x-ray density of this liquid so as to make it stand out in sharp contrast to the fetus and placenta. They injected about 10

c.c. of a 1:1 solution of strontium iodide through the anterior abdominal wall, uterine wall, and fetal membranes into the amniotic sac. After waiting for thirty to sixty minutes, in order to permit even diffusion of the radiopaque medium, they took anteroposterior and lateral films with the patient recumbent. These films, as reproduced in their article, demonstrated clearly the position of the placenta. The fetus was so well outlined that the scrotum in several males was plainly visualized. Proof of the fact that the fetus actively swallows amniotic fluid was demonstrated by a well-outlined radiopaque fetal stomach in every case. Certain films even showed cross sections of loops of umbilical cord encircling the neck and buttocks of the fetus. In their series of twenty-one cases there were no injurious or toxic effects to the mother, but in one case the placenta was perforated and a 6-month fetus was expelled thirty hours later. They made no mention of how many mothers went into labor following the injection.

Kerr and Mackay[8] utilized this method in studying twenty cases of severe bleeding in women whose pregnancy was of twenty-four or more weeks' duration. In the first ten cases they, too, injected strontium iodide, but in three of them, who were in the twenty-fourth week, the fetal movements and heart sounds ceased, and the patients shortly delivered dead fetuses. They injected each of the next ten cases with 20 c.c. of Uroselectan-B, and stated that they were unable to demonstrate that the use of this drug caused any ill effects in the mother or fetus in this short series. They took lateral and anteroposterior views of the uterus thirty minutes after the injection and were able to detect the position of the placenta in eighteen of the twenty cases. Likewise they could demonstrate loops of cord and the fetal scrotum in some films. A subsequent check of the position of the placenta at the time of delivery revealed them to have been correct in each instance as to its localization by x-ray. In ten cases, labor began in from a few hours to five days following the injection. Four of the infants in their series were born during the twenty-fourth week of pregnancy and succumbed. The remaining sixteen survived even though many were premature. This technique was repeated by Burke,[9] whose best results were obtained with the use of Uroselectan-B. In one case the films were used in deciding in favor of cesarean section as a method of delivery, since the lower placental border was seen to encroach upon the general region of the internal cervical os. Since he found that labor was induced by the injection of Uroselectan-B, he used it as a method of induction in twenty-seven additional cases, obtaining successful results in twenty-six of them. The case that failed to go into labor was a patient with hydramnios. The onset of labor followed in from two to seventy-two hours, the average time of elapse being twenty-three and one-half hours.

The chief objections to uterine puncture for amniography are the possible danger of injury to the intestines, and of trauma to the fetus, placenta, or umbilical cord. The taking of such risks is certainly not justified in view of the efficiency of the safer methods of x-ray placentography now in use.

The important milestone in the development of techniques for x-ray visualization of the placenta came with the publication, in January, 1934, of a paper by Snow and Powell.[2] They described the simple procedure of taking anteroposterior and lateral films of the uterus with the patient recumbent. Without any special preparation of the patient, they employed a technique of relatively high voltage and short exposure time, and achieved a sufficient soft-tissue effect to allow ready visualization of the placenta. In the sixty routine cases upon which this method was employed, the position of the placenta was generally demonstrable as a long, elliptical thickening of the uterine wall, not occupied by fetal parts, and lying wholly within the ovoid shadow of the uterus. Snow claimed that the placenta could usually be differentiated from the liquor amnii because, "consisting of tissues and blood, [it] causes greater obstruction to the roentgen rays than the amniotic fluid, which is of low specific gravity." The experience of other workers,[10, 11] including ourselves, has not borne out the possibility of making this fine distinction, but such is seldom necessary except in cases of hydramnios.

One month following the paper by Snow and Powell another major contribution was made by Ude, Weum, and Urner.[3] They reported a case in which an anteroposterior film of the uterus of a woman in the third trimester of pregnancy showed the head displaced upward

from the pelvis and to the right. They also noted that a mass was lying on the left side of the lower uterine segment, and that it extended down beneath the head, coming between it and the bladder. The bladder had only a small amount of urine in it, but was visualized nevertheless. They made the diagnosis of placenta previa, and it was substantiated at cesarean section. This is the first x-ray diagnosis of this condition that we can find in the American literature. In subsequent cases, Ude and his co-workers injected the bladder with sodium iodide solution, thus introducing x-ray cystography as an adjunct aid in the localization of the placenta and the diagnosis of placenta previa.

In the years since the pioneering cited in the foregoing, many other workers have utilized and developed the original methods of Snow and of Ude, but in this country in recent years there have been no published papers reporting the use of the amniography technique of Menees, et al., Kerr and Mackay, and Burke.

In subsequent papers, Snow[12] and Snow and Rosensohn[13] reported the demonstration by x-ray of premature separation of the placenta, late extrauterine pregnancy (in one instance he demonstrated a thickened amniotic sac), some tumors complicating pregnancy, and, when the bladder had been injected with from 150 to 200 c.c. of air, placenta previa. In a further paper on cystography, Ude, Urner, and Robbins[14] reported forty-four new cases in which they injected 40 c.c. of sodium iodide solution into the bladder, and further prepared the patient by low colonic flushes in order to empty the lower bowel of feces and gas. They took 14 by 17 inch anteroposterior films, from which they made the diagnosis of central placenta previa in four cases and partial previa in one, the other thirty-nine being negative for placenta previa. The clinical findings from this group showed that forty cases were negative for placenta previa, while three had central previa and one had partial previa. Their one error was on the positive side and thus was not dangerous. The clinical result of this low incidence of error, state Ude and his co-workers, is that their obstetricians have never been misled into cesarean section, but have often been strongly fortified to proceed with surgery when the suspected clinical findings of placenta previa were confirmed. Surgical procedures should not be carried out solely on the basis of placentography, they warn, and the roentgenologic opinion should be used by the clinician purely as corroborative evidence.

Recent Studies

The literature contains the reports of many other subsequent workers (McIver,[15] McDowell,[16] Hall, Currin and Lynch,[17] Prentiss and Tucker,[18] Beck and Light,[19] Dippel and Brown,[20, 21, 22] Lloyd and Samuel,[23] Buxton, Hunt and Potter,[24] Manges-Smith,[25] McCort, Davidson and Walton,[26] Scheetz, Good and Hunt,[27] and Bishop[10]) who have used either the soft-tissue or cystographic technique, or both. The chief clinical importance of the methods, naturally, is the making of a positive or negative diagnosis of placenta previa. Some have found, in making cystographic studies, that the use of air in the bladder, instead of a radiopaque liquid, is of great advantage in that no part of the fetal head is obscured and a more exact picture of the thickness of the soft tissues between the head and the "black" bladder shadow is obtained on the film. Others advise the use of varying amounts of 12.5 per cent sodium iodide solution, and take anteroposterior, lateral and, sometimes, oblique views. Three writers[19, 24, 10] have reported good results from taking anteroposterior precision stereoscopic films of the bladder, which they found to be of particular advantage in diagnosing placenta previa in cases with breech presentation. On anteroposterior cystographic films, in cephalic presentation without placenta previa, the usual distance of the head from the bladder shadow has been determined[18] to range between 1.1 and 1.3 cm. This space contains the fetal membranes, the wall of the lower uterine segment, the 2 vesical peritoneal layers, and the thickness of the bladder wall itself. When some additional soft-tissue mass is seen to be interposed between the head and the bladder shadow, increasing the distance between them or displacing the head appreciably upward or aside from its usual roughly central position in the pelvis, one must immediately be suspicious of the presence of placenta previa.

The reported success in accurate localization of the placenta in some fairly large series of cases varies roughly between 85 and 97 per cent. In a series of 92 women with third

trimester bleeding, Dippel and Brown,[22] using only the soft-tissue technique, found no errors in their roentgenologic localization of the placenta in the 53 instances in which its position was checked by reliable clinical methods. There were eleven cases of placenta previa in their series, all of which were correctly diagnosed by x-ray. The soft-tissue technique alone, report Buxton, Hunt and Potter,[24] gave accurate visualization of the placenta in 86.1 per cent of a series of 108 cases of painless bleeding in the third trimester. By using the soft-tissue method and cystographic studies where indicated, they were able to locate the placenta accurately in 97.6 per cent of all cases so studied. In this series they had seventeen cases of placenta previa, sixteen of which were correctly diagnosed by x-ray. Bishop[10] states that in properly taken films the diagnosis, "negative for placenta previa," should achieve an accuracy of 97 per cent or better, if care and judgment are exercised in their reading.

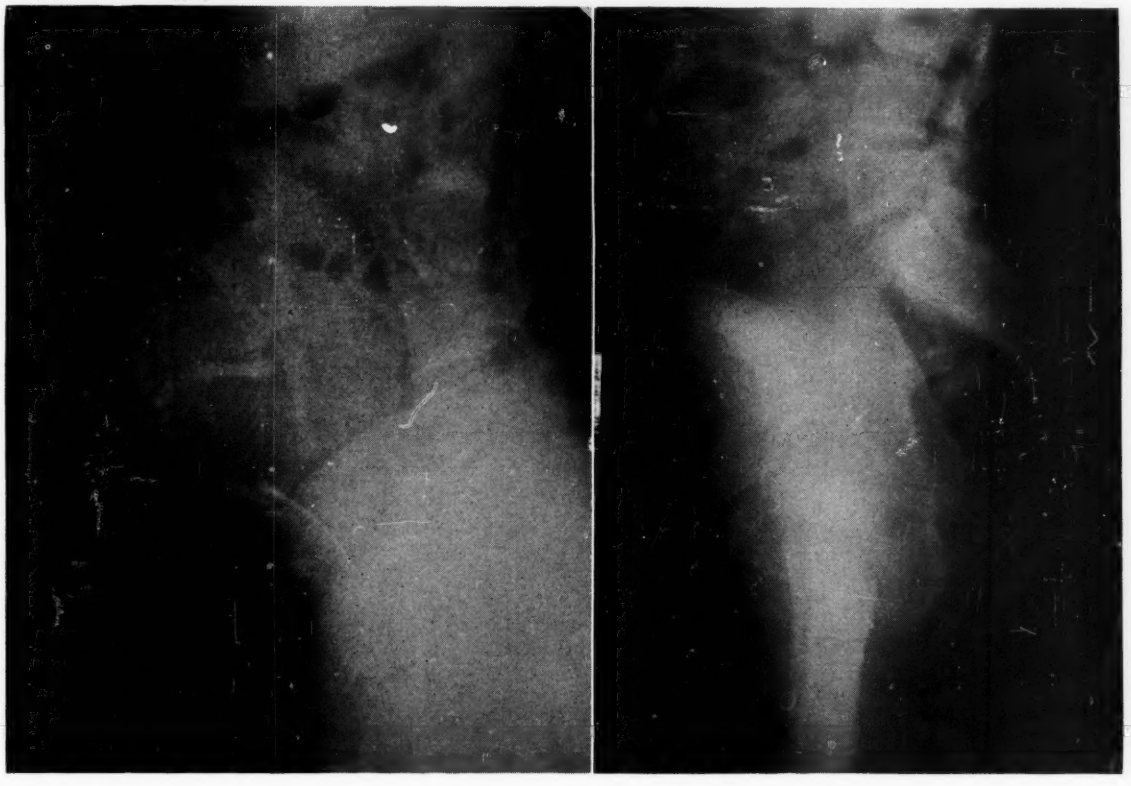
Successful results in x-ray placentography can be obtained only when the obstetrician and roentgenologist work together in a harmonious team. As Matthews[28] stated: "The obstetrician must take the lead and exhibit the proper amount of enthusiasm, for certainly the roentgenologist cannot be expected to know when roentgenography is indicated in a given obstetric case. It would seem, therefore, that the future of this very important help in better diagnosis is entirely in the hands of the obstetrician." "The method requires some study and observation and special interest on the part of the roentgenologist as well as cooperation of the obstetrician to show results," writes Manges-Smith.[25]

Technique

At the Boston Lying-in Hospital we have used an x-ray technique essentially similar to that reported by Dippel and Brown.[20] When compared with the regular technique for taking roentgenograms of the abdomen, it differs chiefly in that a slightly higher voltage and lower exposure time are employed. In taking films of the pregnant uterus with the patient lying flat on the table, we use a regular intensifying screen and a 14 by 17 inch film. We vary our KVP between 75 and 82, depending on the degree, if any, of obesity. With our machine we use 100 Ma. and an exposure time of 1 to 2 seconds, whereas Dippel and Brown used 50 Ma. for 4 seconds. This factor can be varied according to the range of the equipment, but we prefer to use the higher Ma. and the shorter time exposure as it decreases the chance of fetal movement showing on the film. Dippel and Brown used a tube-film distance of 42 inches, whereas we have always taken our films at 40 inches. We employ our regular Potter-Bucky grid, but no filters nor special roentgen-tube equipment are necessary. In developing our films we rely chiefly on time, varying it slightly, if necessary, according to the usual indications. We have not found it necessary to develop the films by sight, as recommended by Carty.[29] Along with other workers in this field, we believe that almost any average x-ray equipment, if properly used, will give adequate soft-tissue films.

We have gradually evolved our technique, and now recommend taking the first film with the patient lying on her side (See Fig. 1, Film *A*). We try to get her to keep her legs unflexed at the hips as much as possible so that the upper thighs will not overlie the lower uterine segment (See Fig. 2, Film *B*). If the first lateral film does not show the placenta, or appears to show only an edge of it, we place the patient on the other side, either with the transverse axis of the pelvis perpendicular to the table top or at some degree of obliquity to it, according to the suggestive findings of the first film. Since about 85 to 90 per cent of placentas lie either on the anterior or posterior wall of the uterus[4, 5, 22] the lateral film is usually sufficient. In some cases, again follow the suggestion of the first film, we take the second plate with the patient lying flat on her back, as this will allow visualization of placentas which lie in part or in whole on a lateral wall of the uterus (See Fig. 3, Film *B*). The whole point is that, in order to have the placenta show on the film, we must endeavor to secure, as nearly as possible,

an edgewise view of its central vertical axis. In some cases, where the presenting part appears to be riding above or to one side of the inlet of the true pelvis, we will take lateral and/or anteroposterior films of the patient in the standing position, and, in most of these cases, providing the patient's bladder is empty, gravity alone will bring the presenting part downward to a closer approximation with the pelvic inlet (See Fig. 1, Film *B*), or may even bring about some engagement of the part. Anterior over-riding of the symphysis pubis by the head has been noted in patients who have relaxed anterior abdominal walls and postural



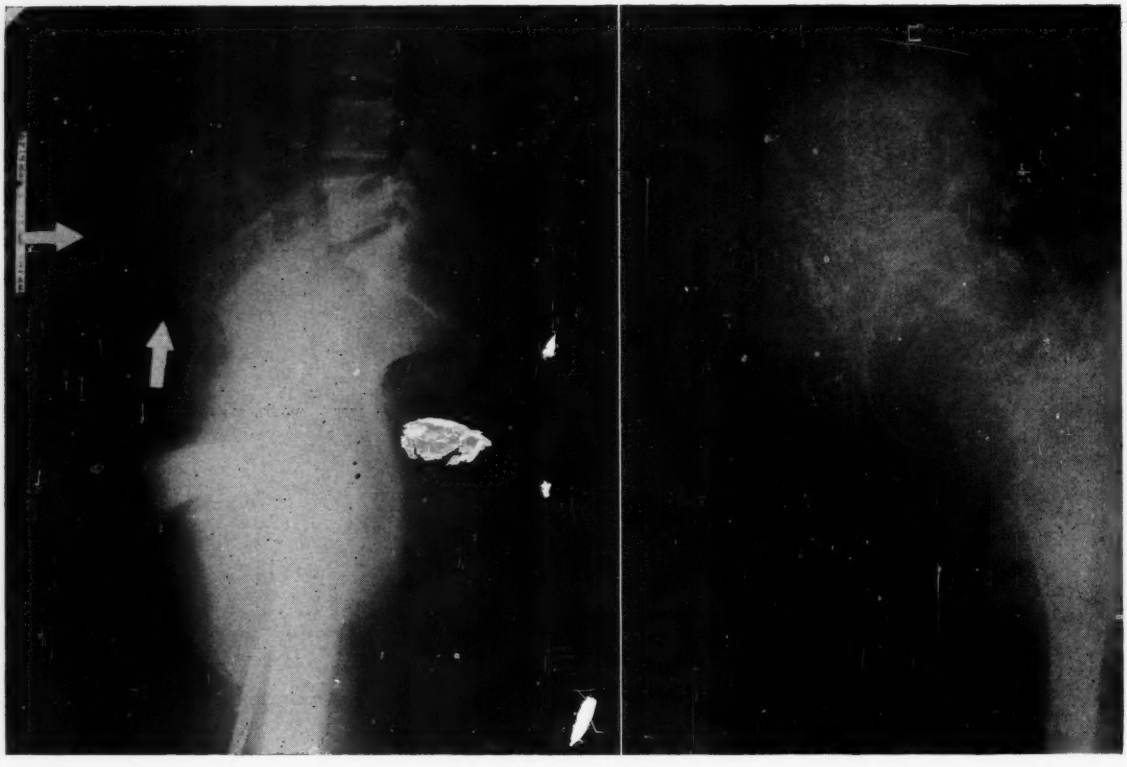
A. *B.*

1. In the two above films the placenta lies low on the posterior uterine wall; they offer a comparison between partial and marginal placenta previa.

Film *A:* C. D., Unit No. 39282, X-ray No. 22981, a 32-year-old gravida ii, para i, had a small amount of painless bright vaginal bleeding in her 25th week, and again in her 31st week, at which time the above x-ray was taken. The roentgenologic diagnosis of 'posterior wall placenta, with partial placenta previa" was made. She bled again, in greater amount, in her 33rd week, and vaginal exmination revealed her to have a partial previa. Immediate classical section was done, and the placenta was found to lie low on the posterior uterine wall and its lower border extended partially across the internal os of the cervix. Mother and baby survived. Note the anterior displacement of the head from the sacral promontory, a distance of 6.5 cm. on the film. The head is not only over-riding the symphysis pubis, but lies 3.5 cm. above it. This film presents a classic picture of low posterior wall placenta with partial previa.

Film *B:* M. C., Unit No. 31166, x-ray No. 25096, a 24-year-old gravida v, para iv, had a painless "sudden gush" of bright blood from the vagina when she was at term, following which the above film was taken. The x-ray diagnosis was "low posterior wall placenta, with marginal placenta previa." There was further bleeding the following day, and at vaginal examination the lower border of the placenta was palpated 2 cm. above the internal os on the posterior wall of the lower uterine segment. Immediate section was done, at which time the placental position was verified. Mother and baby survived. Note the anterior displacement of the head from the sacral promontory (5.5 cm. on the film), and the fact that the head, in contrast to Film *A*, lies directly upon the symphysis pubis. This plate is a typical representation of low posterior wall placenta with marginal previa, and since it was taken with the patient standing the head came down as close to the symphysis pubis as the intervening uterine wall thickness would allow.

hyperextension of the lumbar spine. We usually take standing cystograms in such cases, and occasionally have applied light manual pressure to the appropriate portion of the fetus, thus slightly augmenting the force of gravity in bringing the head down to some degree of approximation with the bladder. If the lower uterine segment is filled in part or in whole by the placenta, the head will remain displaced in some upward direction from the inlet of the pelvic canal as it did in Film *A* in both Figs. 2 and 3.



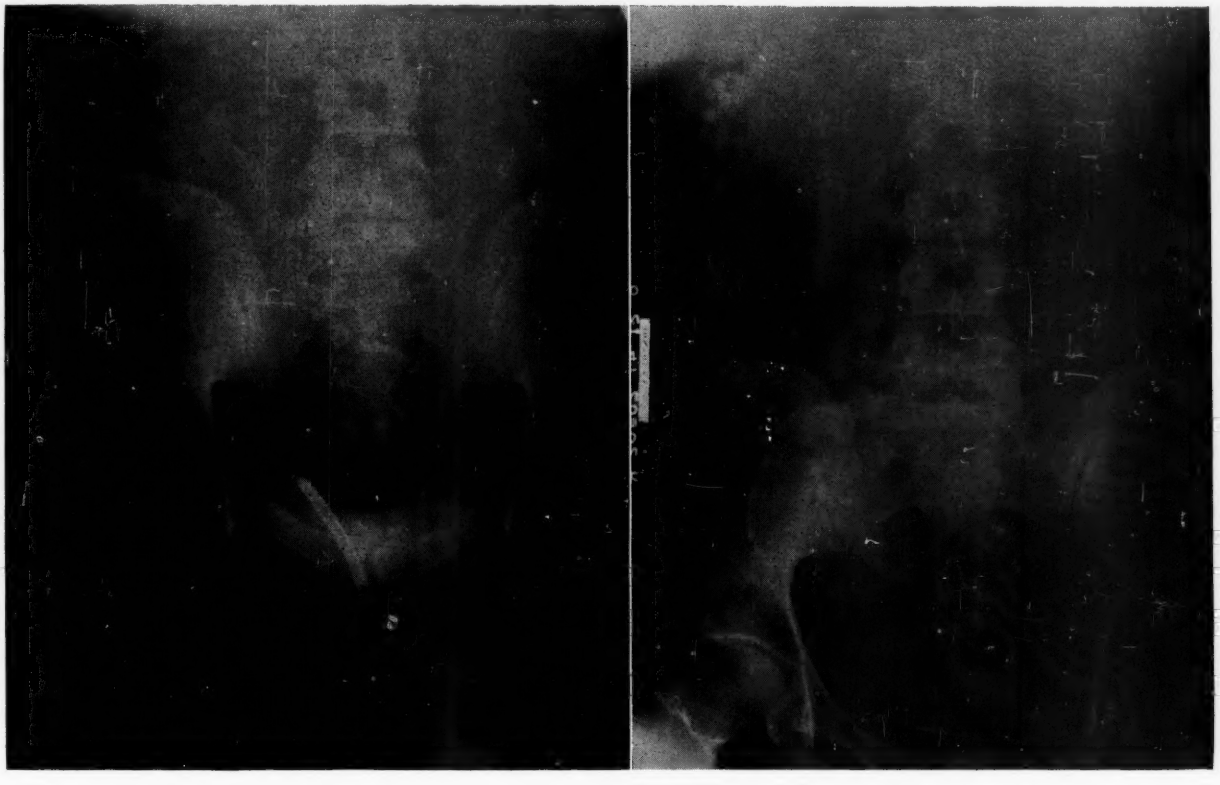
A. *B.*

Fig. 2.—In the two above films the placenta lies low on the anterior uterine wall and they offer a comparison between partial and marginal placenta previs.

Film *A:* M. L., Unit No. 44225, X-ray No. 26248, a 28-year-old gravida ii, para i, had slight vaginal staining in her 21st, 23rd, and 25th weeks of pregnancy. In her 27th week she passed a small amount of bright blood and reported to the Out-Patient Department, where transverse lie of the fetus was discovered. X-ray studies were made, from which it was felt that she probably had placenta previa, with the placenta low-implanted on the anterior uterine wall. At the beginning of her 29th week she had a sudden vaginal hemorrhage, came to the hospital at once, and cystography was carried out (Film *A*). As this standing lateral cystogram shows, the head (outlined by arrows) is "riding" 6.5 cm. (on the film) above the bladder, and 9 cm. above the symphysis pubis. The x-ray diagnosis was "low-implanted anterior wall placenta, with partial previa," which was shortly confirmed at vaginal examination. Brisk bleeding occurred, and a Braxton Hicks version was done, a 2½-pound infant, which succumbed, being shortly delivered. The mother survived without difficulty.

Film *B:* L. K., Unit No. 37826, X-ray No. 24995, a 32-year-old gravida iv, para iii, had vaginal bleeding with cramps in her 30th week of pregnancy, following which episode the above x-ray was taken. The roentgenologic diagnosis was "low implanted anterior wall placenta, with marginal or partial placenta previa." She hd further bleeding at the beginning of her 34th week, following the onset of desultory bleeding, and vaginal examination revealed the lower placental border to lie about 1 cm. above the internal os on the anterior wall of the lower uterine segmnet. Classical section was done at once, at which time the position of the placenta was confirmed. Note the upward displacement of the head (6.5 cm. on the film) from the symphysis pubis, also its relatively normal relation to the sacral promontory (a distance of 2.5 cm.). The placenta is seen to lie over the entire length of the anterior uterine wall, and this film presents a classic picture of anterior wall marginal placenta previa.

We do cystographic studies in cases in which the placenta is not adequately demonstrated in the body or fundus of the uterus by the soft-tissue technique, or when the film suggests that a major portion of the placenta lies in the lower uterine segment, or if the head is displaced upward or to one side of its usual more or less central position in or above the inlet of the pelvic canal. Thus. if there are any findings suggestive of the presence of placenta previa, we do cystography. Our usual method is to inject 100 to 200 c.c. of 12.5 per cent sodium iodide solution into the bladder. We then take an anteroposterior film with the patient lying on her back. If this film is not conclusive, or if we appear to have a placenta lying low on the posterior or anterior wall, we turn



A. *B.*

Fig. 3.—The two above films were taken on the same patient at an interval of six weeks. They show the persistent and similar displacement of the head which is frequently seen in cases of complete placenta previa.

C. S., Unit No. 26248, X-ray No. 25932, a 32-year-old gravida vii, para vi, had sudden, painless vaginal bleeding in her 26th week. She was admitted to the hospital and x-ray studies were made (Film *A*). As Film *A* shows, the left horn of the bladder is depressed lower than the right horn, and the head is displaced upward and to the right. A roentgenologic diagnosis of "low-implanted left lateral wall placenta, with complete placenta previa" was made. The patient was kept in the hospital, and another x-ray was taken at the beginning of her 32nd week (Film *B*). This second film shows the increased size of the fetus, and the head is similarly displaced, but is higher and more to the right, as one would naturally expect in view of its increased size. The soft tissue detail of the lower uterine segment, which appears to be filled by the placenta, is plainly visible in this film. The patient remained in the hospital, and when she was 6 weeks from term she had a sudden profuse painless hemorrhage. Section was done at once, the baby being so delivered 28 minutes following the onset of the bleeding. The placenta was found to lie exactly as pictured in the x-rays, and its lower border covered and extended 2 inches to the right beyond the internal os of the cervix. Mother and baby survived.

Film *A* was taken with the patient standing, and in such a case, where the head still does not settle down into the superior bladder concavity, one can be reasonably certain that it is displaced therefrom by some soft tissue mass which is occupying the lower part of the lower uterine segment. This case also illustrates the necessity of taking anteroposterior views of the uterus in order to visualize the occasional placenta implanted on a lateral uterine wall. The lateral films in this case did not show the placenta, and were of value only insofar as they thereby suggested a lateral wall implantation.

the patient on her side and take a lateral cystogram. If these two films are unsatisfactory, or if the presenting part is riding too high above the bladder, we will take anteroposterior (Film *A*, Fig. 3) and, if indicated, lateral views (Film *A*, Fig. 2) of the bladder with the patient standing. If the sigmoid is filled with feces and obscures the relationships of the lateral cystogram, we gently flush it out and put some air in it. This procedure is of particular value in cases where there is a low posterior wall placenta as the air-filled sigmoid allows greater definition of the posterior half of the lower uterine segment. It is very seldom that these measures will not allow one to rule in or out the presence of placenta previa, particularly if the duration of the pregnancy is thirty-four weeks or more.

The films are read and reported by the Resident Obstetrician. A small percentage of them are also taken by the Resident Staff, but most are taken by our regular technicians. Our x-ray department is on the delivery floor, and at any time, day or night, we can obtain x-ray studies on our patients within a few minutes. We believe that this is an ideal system, both in treating our patients and in training our Resident and House Staffs.

Studies and Results

We have studied the films taken on 488 women for localization of the placenta during 1945, 1946, and 1947. Four hundred thirty-two of these were patients with uterine bleeding occurring in the third trimester. The other fifty-six cases were x-rayed because of persistent transverse or oblique position of the fetus in the last ten weeks of pregnancy. The 432 cases of bleeding occurred during a period in which there were 14,166 deliveries after viability. Hence 3.05 per cent of all patients had x-ray studies because of uterine bleeding.*

In our series of 488 women who were x-rayed, the films on 14 did not allow our visualization of the placenta because the pregnancy was too early to allow adequate definition, because of the presence of twins or marked hydramnios, or as the result of technical error. Thus we finally had readable films on 474 women, and they constitute the series here reported.

In 414 cases, or 87.3 per cent, we were able to make the diagnosis, "negative for placenta previa," from the first soft-tissue films without difficulty, and in this group we cannot discover any evidence that we missed a single case of placenta previa. In the other 60 cases, or 12.7 per cent, we resorted to further films, cystograms, or more intensive study of the original plates because of obvious or suggestive evidences of placenta previa. The roentgenologic diagnoses resulting from our deliberations on the total series are represented in Table I. For the special purposes of this study all of the x-ray diagnoses presented in this table were made without knowledge of the actual clinical findings, and the only history known was the patient's parity, expected date of confinement, and the fact that she had had some bleeding (except in the films which showed transverse position of the fetus). All clinical findings were determined either at delivery, at sterile vaginal "double set-up" examination, or at cesarean section.

In our total series, we had 39 cases of placenta previa, complete previa being present in 21 women, partial previa in 8, and marginal previa in 10. Not included in our series are 10 additional cases of placenta previa which occurred during the period covered by this study. These patients, on arrival at the hospital, were bled out or in shock. Their condition was such that emergency transfusion, vaginal examination, and cesarean section were indicated, and we did not subject them to the loss of time that x-ray studies would have necessitated.

*Our hospital records show that about 87.5 per cent of the cases of uterine bleeding in the third trimester had x-ray studies, and thus, by interpolation, we can derive a figure of about 3.48 per cent for the incidence of third trimester uterine bleeding in our clinic as a whole.

The most dangerous mistake one can make in diagnosing these films, obviously, is to say, in any given case, that the plate is "negative for placenta previa" when, in actual fact, the woman does have this condition. As Table I shows, we made this serious mistake in three cases. In each case, however, the degree of previa was only marginal. Table II shows an analysis of these cases.

TABLE I. ACCURACY OF ROENTGENOLOGIC DIAGNOSIS OF PRESENCE OR ABSENCE OF PLACENTA PREVIA IN A SERIES OF 474 CASES

		CASES DIAGNOSED "NEGATIVE FOR PLACENTA PREVIA"		CASES DIAGNOSED "POSITIVE FOR PLACENTA PREVIA"	
	NUMBER OF CASES	DIAGNOSIS CORRECT	DIAGNOSIS INCORRECT	DIAGNOSIS CORRECT	DIAGNOSIS INCORRECT
A. Cases readily diagnosed from first films*	414 or 87.3 per cent	414	none	none	none
B. Cases suggestive of placenta previa, and given further x-ray study and/or deliberations†	60 or 12.7 per cent	14	3	37	6
Totals		428	3	37	6
Diagnostic error		0.7 per cent		16.2 per cent	
Total correct diagnoses		465			
Total incorrect diagnoses		9			
Total diagnostic error		1.9 per cent			

*No special clinical check-up was made as to the true location of the placenta in these cases, but at delivery there was nothing to suggest that some degree of placenta previa had been present.

†Actual position of placenta was determined in this group, either by sterile vaginal examination or at cesarean section.

As Table I shows, we made the incorrect positive diagnosis of placenta previa in six cases. While the false positive diagnoses constitute technical errors in the method itself, they are not potentially dangerous to the patient. Table III shows an analysis of these cases.

The obvious fact disclosed in Tables II and III is that we were able to diagnose complete, or central, placenta previa correctly in all of the 21 instances in which it occurred in our series of 474 cases. All of the eight women who had partial placenta previa also were correctly diagnosed. We made false negative diagnoses in three of the ten cases in which marginal placenta previa was present. No incorrect positive diagnoses for complete placenta previa were made, but we did make one for partial previa, and five for marginal previa.

In two of our three false negative diagnoses (see Table II) we underestimated how far down the lower border of the placenta extended on the posterior wall of the lower uterine segment, and this particular situation thus constituted, for practical purposes, our chief diagnostic pitfall.

In our six false positive diagnoses (see Table III) we overestimated how far the edge of the placenta extended downward when it was implanted low on the anterior wall in four of the cases, and we made the same error in two cases when it was low on the posterior wall.

We did not make any incorrect diagnoses from our cystogram films. In the cases in which we resorted to this technique, we confirmed the presence of placenta previa in 39 per cent, ruled it out in 50 per cent, and confirmed low implantation in 11 per cent. Cystographic studies were not done on any of the three cases represented in Table II, because in two of them (Cases 1 and 2) the clinical picture was obviously that of placenta previa until proved otherwise by sterile vaginal "double set-up" examination. These two cases required immediate emergency measures and there was neither the need nor the time for further

x-ray studies. In the third case in Table II (No. 3), cystography was not done because the patient had a second bout of bleeding one week following her first episode, and sterile vaginal examination was decided upon and carried out forthwith.

TABLE II. ANALYSIS OF THE 3 CASES OF MARGINAL PLACENTA PREVIA IN WHICH INCORRECT ROENTGENOLOGIC DIAGNOSIS WAS MADE

	NUMBER OF WEEKS PREGNANT AT TIME OF X-RAY	POSITION OF PLACENTA AS DIAGNOSED BY X-RAY	POSITION OF PLACENTA AS DETERMINED CLINICALLY	TYPE AND AMOUNT OF VAGINAL BLEEDING	TREATMENT	OUTCOME FOR MOTHER AND INFANT
1. M. S., X-ray No. 23,314; Unit Hist. No. 41,718	32	Low-implanted on posterior uterine wall	Low-implanted on posterior uterine wall, with lower border 2½ cm. above internal os when 2 cm. dilated	Sudden painless bleeding of 300 c.c. with subsequent continuous trickle	Despite x-ray diagnosis, clinical picture clearly indicated need of vaginal examination, which was done and followed by section	Both survived
2. E. B., X-ray No. 23,487; Unit Hist. No. 37,205	32	Low-implanted on posterior, and partly on left lateral uterine wall. Questionable marginal placenta previa	Low-implanted on posterior and left lateral uterine wall, lower border lying almost at internal os	Sudden painless bleeding of 400 c.c. with subsequent continuous trickle	Despite x-ray diagnosis, patient's clinical condition clearly indicated need of section, which was done at once	Both survived
3. M. C., X-ray No. 24,760; Unit Hist. No. 42,925	29½	Low-implanted on anterior uterine wall	Marginal previa, placenta low-implanted on anterior uterine wall	"Several sudden gushes" at 29½ weeks, followed by another sudden flow at 30½ weeks	Vaginal examination done at 30½ weeks, and No. 5 bag inserted. Normal spontaneous delivery resulted	Mother survived. Infant weighed 2 pounds 12 ounces at birth, died of prematurity

As far as the outcome was concerned in the nine cases we diagnosed incorrectly, all of the mothers survived and there was no avoidable fetal mortality. Our x-ray diagnoses, as to placental position, were correct in 98.1 per cent of the 474 cases, which is practically the same rate as was achieved by Buxton et al.[24] and by Bishop.[10] If we count the previously mentioned unreadable films taken on fourteen women as diagnostic failures, our method in the total series of 488 cases achieves a correctness of 95.3 per cent.

As has been stated, only 432 of the women in our series were x-rayed because of vaginal bleeding. The other 56 cases had routine x-ray studies solely because of the discovery, during routine palpation in the Out-patient Department, of persistent transverse or oblique position of the fetus in the last ten weeks of pregnancy. We have followed this practice at the Boston Lying-in Hospital for several years, and have found that transverse position of the fetus has been noted clinically, or by x-ray, in about one-third of our cases of placenta previa. Such fetal position, thus, is a particularly important diagnostic sign in placenta previa.[30]

Of the 56 patients in our series who had transverse or oblique position of the fetus, 12, or 21.4 per cent, had placenta previa. Breech presentation was found in 53 women, and, of these, three had placenta previa, all of which conditions were correctly diagnosed by x-ray. Three hundred sixty-seven cases had cephalic presentation, in twenty-four of which there was placenta previa. Two of the incorrect negative diagnoses for placenta previa (Cases 1 and 2, Table II) were made in women with cephalic presentation, while the third (Case 3, Table II) was made in a woman who had transverse position of the fetus at the time the film was taken.

TABLE III. ANALYSIS OF 6 CASES INCORRECTLY DIAGNOSED AS HAVING PLACENTA PREVIA

	NUMBER OF WEEKS PREGNANT AT TIME OF X-RAY	POSITION OF PLACENTA AS DIAGNOSED BY X-RAY	POSITION OF PLACENTA AS DETERMINED CLINICALLY	TYPE AND AMOUNT OF VAGINAL BLEEDING	TREATMENT	OUTCOME FOR MOTHER AND INFANT
1. H. P., X-ray No. 21,047; Unit Hist. No. 39,676	40	Low—implanted on posterior wall, with marginal previa	Character of labor and delivery excluded previa	Slight spotting	Spontaneous onset of labor. Normal low forceps delivery	Both survived
2. P. E., X-ray No. 23,045; Unit Hist. No. 16,565	33½	Marginal or partial previa, placenta low on posterior wall	Vaginal examination done, no placenta previa found	Slight spotting at 22 weeks, at 33½ weeks, and at 35 weeks	Spontaneous onset of labor, with low forceps delivery at 35½ weeks	Both survived
3. C. C., X-ray No. 23,337; Unit Hist. No. 23,063	31½	Low—implanted on anterior uterine wall, with marginal previa	Normal character of labor and delivery excluded previa	None. X-rays taken because of persistent transverse position of fetus	Spontaneous correction of fetal position to cephalic presentation occurred. Normal spontaneous delivery at term	Both survived
4. E. S., X-ray No. 23,486; Unit Hist. No. 10,560	27½	Low—implanted on anterior uterine wall, with marginal previa	Low—implanted on anterior wall, but not a marginal previa	Moderate bleeding off and on for 3 days (had anemia and Grade I pre-eclampsia)	Uterus tense and tender. Clinical picture was that of partial premature toxic separation of placenta. No previa found at vaginal examination. Section done	Mother survived. Infant's birth weight, 2 pounds, 8 ounces. Died of prematurity
5. G. E., X-ray No. 24,147; Unit Hist. No. 8,000	30	Low—implanted on anterior wall, with marginal previa	Normal character of labor and delivery excluded previa	None. X-rays taken because of persistent transverse position of fetus	Spontaneous onset of labor, with normal spontaneous delivery at term	Both survived
6. G. L., X-ray No. 24,425; Unit Hist. No. 18,543	34	Low—implanted on anterior wall, with marginal previa	Normal character of labor and delivery excluded previa	Very slight spotting at 34 weeks	Spontaneous onset of labor, with normal spontaneous delivery at term	Both survived

Discussion

The figures denoting the accuracy of x-ray localization of the placenta generally have been impressive. In this paper, they turned out to be far better than we had expected when the study was in progress. We were certainly not sure of our diagnosis in quite a few of the cases, but this feeling has been some-

what allayed by the fact that we subsequently were proved to have been correct in 98 per cent of the instances. It is difficult to feel sure of a diagnosis when one is making it largely on negative instead of positive evidence, as is usually the case in this work. The reading of soft-tissue films of the pregnant uterus is in a different category from reading a plate showing a fractured femur. In the case of the fracture, one is able to make a straightforward *diagnosis* on positive evidence. It is quite the opposite with soft-tissue films of pregnancy, for in them one is merely able to cite an *impression* or an opinion as to where the placenta lies.

We have encountered many pitfalls, as have others,[18, 21, 24] in interpreting our films. In a first film, we have found the head riding high above the inlet and over-riding the symphysis in cases in which the patient merely had a bladder full of urine. In these instances we have had the patient empty her bladder, have injected it with about 100 c.c. of sodium iodide solution, and have taken a lateral standing cystogram. A rectosigmoid full of soft feces can produce much the same picture.

In the multigravid patient with marked relaxation of the anterior abdominal wall, there can be some anterior and upward "floating" of the head away from the pelvic inlet when she lies on her side on the x-ray table.[30] In such a case, a standing lateral film, with, if necessary, some light manual pressure exerted downward on the upper fetal pole, usually brings the presenting part down to a position in which it "rests on the bottom" of the lower uterine segment, and the true anatomic situation then can be correctly pictured.

The localization of the placenta in twin pregnancies is difficult, and, in our series, in the several instances in which this condition was encountered, we were not able to visualize it definitely. The same was true in cases with marked hydramnios and in normal pregnancies of a duration of less than 27 weeks. The delineation of the placenta is much more accurate and reliable in pregnancies of 32 or more weeks, and this is particularly true in cystography. It is unusual for a cystogram to be as accurate at 26 weeks of pregnancy as that pictured (Film *A*) in Fig. 3, and in any case earlier than 32 weeks cystography is best done with the patient standing. Nonobservance of this rule may give a misleading representation of the actual anatomic relationships. If the anteroposterior film is not conclusive, a lateral cystogram also should be taken.

It is difficult to demonstrate exactly what benefit our clinic has derived from the adjunct diagnostic aid this x-ray technique has given us. We can state, however, that in a recent sampling series of 56 cases of placenta previa we had no maternal mortality, and that 21 per cent of those cases that had complete previa (they had transverse position of the fetus) were diagnosed by x-ray and had cesarean section before any vaginal bleeding had occurred. Seventy per cent of the infants in this sampling series survived, 14 per cent were stillborn, neonatal death occurred in 14 per cent (chiefly from prematurity), and 2 per cent were nonviable.

At every prenatal visit, each patient is specifically asked if she has had any vaginal staining or bleeding. If she answers in the affirmative and is at or beyond her 26th to 28th week of pregnancy, routine soft-tissue x-ray studies are

made. If we feel relatively certain, from our study of the films, that there is no placenta previa present, we send the patient home with whatever instructions are indicated. It is a relief to us not to have to admit such a case of slight vaginal staining to the hospital for a period of observation, and it is also a financial saving for her. Furthermore, we do not thus tie up any of our beds in such needless fashion, and we are able to rest secure in our minds that she has no more than 1 chance in 50 of having placenta previa. By the same token if the x-rays are positive for placenta previa, we keep her in the hospital and permit her to approach fetal viability as nearly as her clinical course, with safety to her, will allow us (see case report under Fig. 3).

Our method also gives us a rapid and simple means, in cases of third trimester bleeding, of differentiating between placenta previa and partial premature separation of a normally implanted placenta. Once this point is settled we can proceed with the indicated course of treatment.

We do not intend, in any wise, to convey the impression that x-ray studies of the placental position should supplant vaginal examination in the diagnosis of placenta previa. Our experience has taught us, however, that the foreknowledge supplied by our x-ray studies has undoubtedly helped us to avoid an appreciable degree of hemorrhage following vaginal examination, when such examination has been made with a mental picture of the apparent position of the placenta already in mind.

X-ray localization of the placenta, as a routine in our hospital, has been successfully carried out over a continuous period of several years, chiefly because of the genuine interest of the Visiting and Resident Staffs in the method. They have maintained this interest because the method has served them well. In view of the facts that special or inordinately expensive x-ray equipment is not necessary, that any technician and members of the Resident Staff can be taught to take the films, and that a Resident Obstetrician can be taught to read the films, we feel that this method is practical for use in many hospitals in which it is not now being employed. If a careful and conscientious attitude is exercised by the technician taking the films and the doctors who read them, they will be much gratified by the long-range beneficial results it is possible to attain.

Conclusions

1. The history of the development of the methods of x-ray visualization has been traced.

2. The x-ray technique employed at the Boston Lying-in Hospital has been described, and our routine methods of securing the various x-ray views of the pregnant uterus in the last trimester have been outlined in detail. The chief objective, we have found, is to position the patient in such fashion that an edgewise view of the central vertical axis of the placenta will be represented on the film.

3. Our method of taking x-ray cystograms has been described, and the indications for so doing have been stated.

4. We were unable to visualize the placenta in the x-ray films of fourteen women in our total series of 488 cases, but even though we counted these failures

of method in with our diagnostic failures, we still achieved a correctness of 95.3 per cent in localization of the placenta insofar as ruling in or out placenta previa is concerned. In the series of 474 cases in which the placenta was visualized, we made the correct diagnosis of presence or absence of placenta previa in 98.1 per cent.

5. There were 39 cases of placenta previa in our series, and we diagnosed all of these correctly except in three instances in which marginal placenta previa was present. This gave us a correct diagnostic achievement of 100 per cent in complete previa (21 cases), of 100 per cent in partial previa (8 cases), and of 70 per cent in marginal previa (10 cases). This demonstrates that accuracy in the differential x-ray diagnosis between marginal placenta previa and low-implanted placenta was, in our hands, difficult to attain. No maternal mortality, and no increase in fetal or neonatal mortality resulted from our three "false negative" diagnostic errors.

6. We made no incorrect diagnoses in cases in which cystography was done. We were not able to do cystographic studies in the three cases of diagnostic failure for reasons which we have explained. In doubtful cases, we have achieved good results by obtaining both anteroposterior and lateral cystograms of the patient when in standing position.

7. We have had difficulty in visualizing the placenta in cases of twins, marked hydramnios, and in normal pregnancies of a duration of less than 27 weeks.

8. We have presented, as evidence of the beneficial diagnostic aid this x-ray technique has given us, the fact that in a recent sampling series of 56 cases of placenta previa we have had no maternal mortality, and that 21 per cent of the cases of complete previa were diagnosed and treated before any vaginal bleeding had occurred.

9. Since special x-ray equipment is not necessary in carrying out these studies, since the x-ray technique is simple, and since the Resident Obstetrician or any interested roentgenologist can learn to read the films, we believe that this method is a useful aid in the diagnosis of the cause of uterine bleeding in the latter weeks of pregnancy.

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SADDLE BLOCK ANESTHESIA*

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IN THE past two years saddle block anesthesia in obstetrics has gained widespread popularity. Numerous articles have appeared in the recent literature and all are enthusiastic about its use. Our preliminary report was made in 1947.[1] It seems appropriate, therefore, to review our two years' experience and make a final report regarding the suitability of this anesthetic procedure in obstetrical cases.

Material Studied

Since Sept. 6, 1946, heavy Nupercaine saddle block anesthesia† has been used in more than 1,200 selected cases delivered on the obstetrical teaching service of the Stritch School of Medicine, Loyola University. This service includes the Lewis Memorial Maternity Hospital, Mercy Hospital, St. Vincent's Infant and Maternity Hospital, and Misericordia Hospital. For the sake of uniformity of analyses, only the 877 cases delivered at the Lewis Memorial Maternity Hospital will be presented.

The pharmacology of "heavy nupercaine," the technique of administration, and the contraindications for this procedure have been mentioned in our previous report and need not be reiterated. The time of administration was the late first stage or the early second stage of labor. The dosage for most cases was 2.5 mg. and was repeated in only 36 cases, or 4 per cent.

Results

The success of the procedure was based solely on the degree of subjective relief obtained by the mother and not on the level of anesthesia. Thus, we have classed as "incompletely relieved" those patients in whom saddle block anesthesia was present, but in whom some pain was perceived; and as "failures" those patients claiming "no relief," even though sufficient perineal anesthesia was present to permit episiorraphy.

In Fig. 1 the results of the 877 cases are depicted graphically. Eight hundred sixteen, or 93 per cent, of the mothers had complete subjective relief for over one hour; 53, or 6 per cent, obtained incomplete subjective relief, and eight, or 1 per cent, were classed as failures.

As may be seen from Fig. 2, 754 patients, or 86 per cent, of the 877 were delivered solely under the effect of saddle block anesthesia; 38 of these cases, however, were patients with "incomplete relief." The degree of analgesia was sufficient to permit delivery without the patient's requesting supplementary anesthesia.

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*Read before the Fifty-Ninth Annual Meeting of the American Association of Obstetricians, Gynecologists and Abdominal Surgeons at Hot Springs, Virginia, Sept. 9, 10, and 11, 1948.

†Heavy Nupercaine Solution was supplied by Ciba Pharmaceutical Products, Inc., Summit, N. J.

Supplementary delivery anesthetic was used in 123 patients, or 14 per cent. The two most important indications for this procedure were (1) to supplement waning spinal effect in patients delivering later than one and one-half to two hours after the administration of the nupercaine solution; and (2) to provide deeper anesthesia prophylactically for such operative procedures as forceps rotation (particularly Scanzoni maneuver), midforceps delivery, breech decomposition and extraction, version and extraction, etc. As has been pointed out previously, this latter is in keeping with the observation of Malpas of Liverpool that "under spinal anesthesia, the myometrium of the pregnant uterus exhibits heightened reactivity to various stimuli." The third reason for the supplementary delivery anesthetic was for psychological purpose. Light inhalation anesthetic was given to allay the fear and apprehension associated by some patients with the obstetrical procedures. These patients wished to be asleep at the time of delivery.

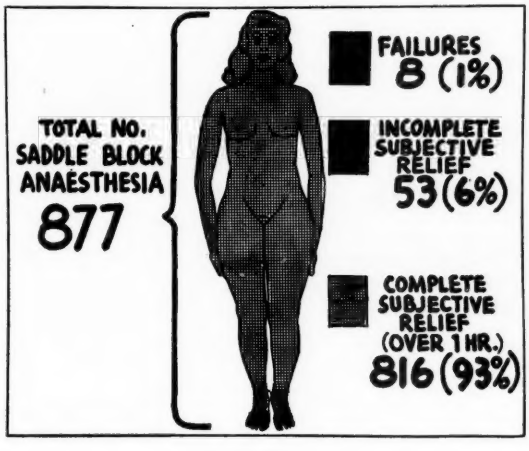

Fig. 1.

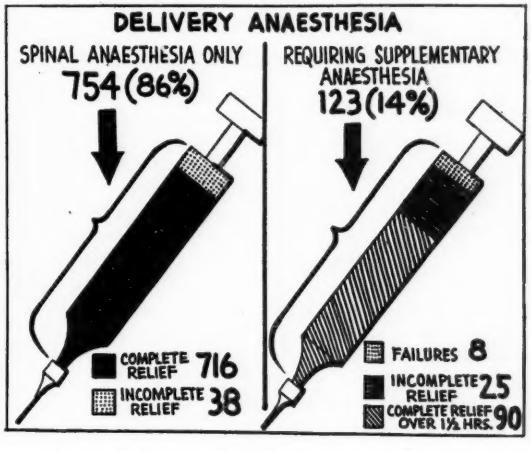

Fig. 2.

In two of the eight cases listed as failures, perineal anesthesia sufficient to permit episiotomy and episiorrhaphy was present, but as the patients stated they had had "no subjective relief" from labor pain, these could not be included in the "incomplete relief" group.

The duration of subjective relief varied from one hour to five hours, but the average was one to two hours. In general, prolonged relief was looked upon with suspicion as possible interference with the progress of labor. Our aim was to administer saddle block anesthesia when delivery was expected to occur within the following two hours.

The objective anesthetic effect, particularly on the perineum, generally exceeded three hours. An extreme of ten hours in one and seven hours and twenty-two minutes in another were noted in two cases early in the series. In these two cases, the perineal anesthesia was sufficient to permit episiorrhaphy.

The manner of deliveries is shown in Fig. 3. In our practice, the use of "prophylactic outlet forceps" is routine, and this type of delivery constitutes the major part of our cases. That a patient with complete subjective relief can be delivered spontaneously solely under the effect of saddle block anesthesia is shown by the 78 cases so delivered. Spontaneous deliveries could replace outlet forceps deliveries by having the patient "bear down" at the time of uterine contractions. Since the contractions are painless, the onset of uterine contraction must be detected by the patient's own hand on the abdomen, or by the ob-

stetrician, so that the accessary delivery forces may be synchronized with the expulsive force of the uterine muscles.

Condition of the infants at birth is shown in Fig. 4. There were 44 infants with birth weights under 5 pounds, 10 ounces, and these were arbitrarily grouped as "prematures." Unfortunately, the fate of these premature infants

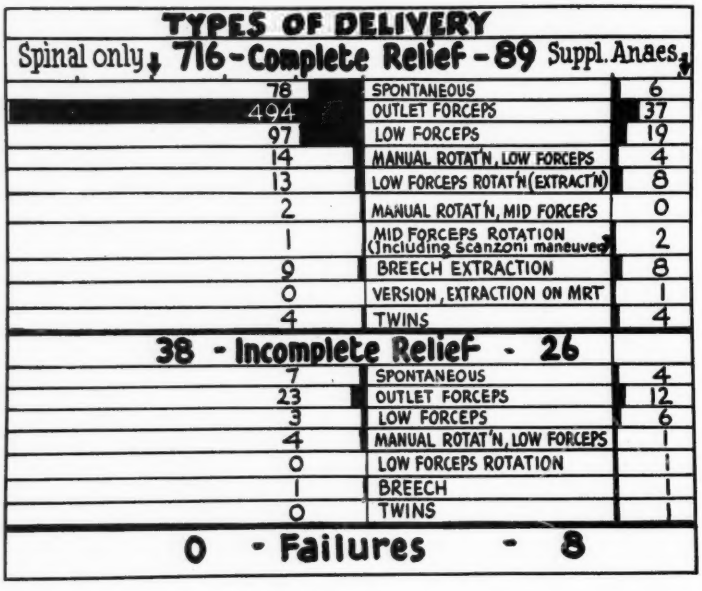

Fig. 3.

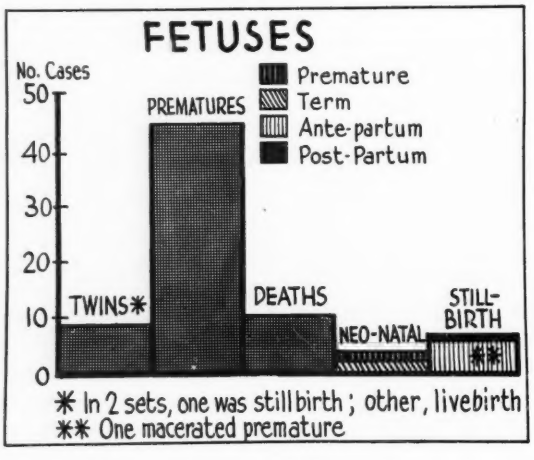

Fig. 4.

cannot be evaluated as the Chicago Board of Health Rules, set up by the American Committee on Maternal Welfare, required their transfer to hospitals with facilities for the care of prematures. There were four neo-natal deaths, and prematurity was the cause in two cases. Of the term infants, one infant weighed 10 pounds, ½ ounce at birth and was delivered in good condition as an "assisted breech" under supplementary ether anesthesia, but died two days later. Autopsy showed only cerebral edema and atelectasis. The second term infant weighed

6 pounds, 12 ounces at birth and was in good condition, but died twenty-four hours later. Of the six stillbirths, two occurred in two sets of twins. In each set one of the twins was macerated. Another of the stillbirths was a macerated premature infant weighing 4 pounds, 3 ounces.

The weight of the "prematures" is shown on Fig. 5.

TABLE I

UNTOWARD EFFECTS

	NO. CASES	PCT
Untoward weakness (Slight to complete paralysis)	869	100%
Effect on Blood Pressure		
Drop less than 20 mg. Hg	721	
" more " " " "	156	18%
Spinal Reaction (?sensitivity to drug)	1	
Post spinal headaches	125	14%
Neurological complications: Foot drop	1	

Table I lists the untoward effects of saddle block anesthesia. Motor weakness was present in 100 per cent of cases listed as completely or incompletely relieved. The degree of motor palsy varied from mild weakness to complete paralysis of the legs. These were all transient and caused no inconveniences. Significant drop in blood pressure of more than 20 mm. was noted in 156 patients, or 18 per cent, but in only 77 did the systolic pressure fall below 100 mm. level. In nine cases the pressure dropped below 80 mm. All, however, responded readily to ephedrine and oxygen therapy. There was one case which we considered a "spinal reaction" and attributed to drug sensitivity. This case has been reviewed in our preliminary report. The neurologic complication of foot drop was also reported previously. Recovery from this complication was spontaneous and complete by the tenth postpartum day.

An analysis of cases with blood pressure fall below 100 mm. systolic pressure is shown in Fig. 6.

Postspinal headache occurred in 14 per cent of the cases and the day of occurrence is shown on Fig. 7. This undesirable side effect continues to present a big problem. The cause of these headaches is as yet unknown. That it is not specifically caused by Nupercaine solution is indicated by the occurrence of identical headache following diagnostic spinal fluid aspiration. Furthermore, the 19.5 per cent incidence of headache with heavy Pontocaine spinal anesthesia reported by Ahearn and Huston,[2] and 14.5 per cent incidence reported by Dieckmann and his associates[3] with Metycaine, Novocain, and Pontocaine, as well as Nupercaine, suggest that the headache is not specific to the agent used.

Our attempt at prophylaxis with ephedrine administration, minimization of spinal fluid loss at the time of spinal puncture, and early assumption of upright position from the day of delivery have not reduced the incidence of postspinal headache. Characteristically, the headache is aggravated by upright position and relieved by lying down, but we have not kept any patient flat in bed for six to seven days in an attempted prophylaxis against developing postspinal headache.

Therapeutically, we have tried ephedrine, antihistaminic substances, 500 c.c. of 20 per cent glucose intravenously, caffeine, etc., as well as the usual analgesics, without consistent results. We are still seeking an effective prophylactic or therapeutic agent.

There have been five instances of retained placenta. We do not believe the use of saddle block anesthesia contributed in any way to this retention.

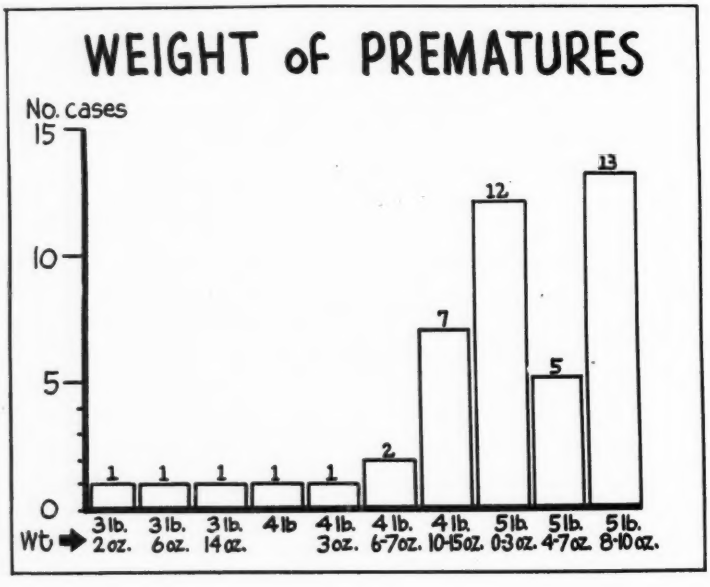

Fig. 5.

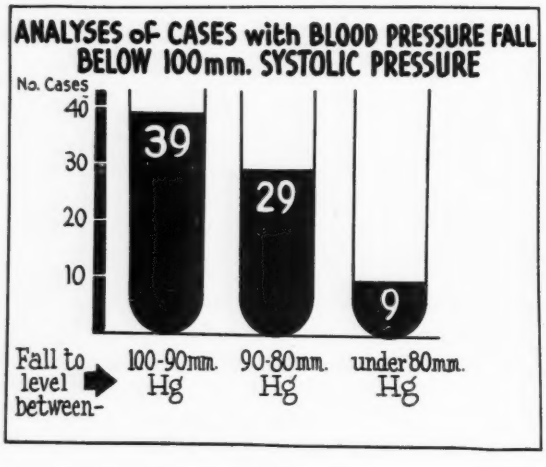

Fig. 6.

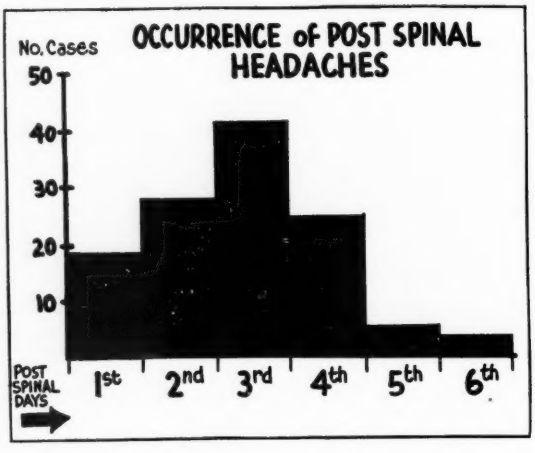

Fig. 7.

Discussion

Saddle block anesthesia has a very definite place in obstetrics, particularly in the second stage of labor. It should not, however, be used to the exclusion of all other forms of analgesic-anesthetic agent. The ideal obstetrical analgesic

agent is the one which will provide absolute safety for both the fetus and mother, complete subjective comfort for the mother, noninterference with the progress of labor, complete absence of undesirable side effect, simplicity and ease of administration, and facilitate the care of obstetrical patients. Saddle block anesthesia is not the ideal method, but is at present closest to this ideal. Spinal anesthesia is potentially dangerous, and hence should not be used by the inexperienced physician nor by an obstetrician who will not take cognizance of the potential danger and exercise all precautions.

Neurological complication, although rare, is always potentially present, as pointed out by Nicholson and Eversole,[4] and was illustrated by our case with foot drop noted on attempted ambulation on the third postpartum day. Trauma to the nerve or cord may be suggested by radiating pain or bloody tap. A previously anesthetized nerve or cord is not capable of causing radiating pain. This is one of the most important reasons for our reluctance to repeat the spinal injection in a patient where some anesthesia is present. Impurities, deterioration, and contamination are the other causes of neurologic complication.

Postspinal headaches may be severe enough to cause worry to the physician. There have been a few instances of severe headaches accompanied by neck stiffness to suggest meningismus. These headaches justify the attitude of some patients in refusing this form of analgesia. The 14 per cent incidence of postspinal headache is too high and too disturbing to label saddle block anesthesia, with the present available agents, as the ideal obstetrical agent.

Other manifestations demanding utmost care and precaution are the drug sensitivity and the effect on the blood pressure. Drug sensitivity may threaten the life of the mother and baby and needs no elaboration. The fall in blood pressure, however, may be disregarded by the inexperienced physician, and hence needs emphasis. Hingson et al.[5] have pointed out that with maternal pressure remaining below 80 mm. Hg systolic, fetal anoxia may be demonstrable in every case where this condition is allowed to exist for five minutes or longer. He believes that the pressure due to resting and contracting uterine tone is greater than the arterial pressure (of below 80 mm. Hg). Failure to prevent or treat promptly the fall in blood pressure may result in irreparable damage to the fetus. *A live child does not signify an undamaged brain.* The anesthetist is responsible for the preventable cerebral damage even when such manifestation occurs later in life.

We have dwelt at length on the danger of spinal anesthesia to emphasize the need of proper precaution. To a qualified anesthetist-obstetrician this method of obstetrical analgesia has been most nearly ideal. Careful evaluation and selection of the patient, exercise of proper precaution (such as testing for drug sensitivity, etc.) and the use of single-dose method (given at the optimum time) have minimized the danger both to the mother and the fetus. Our routine is as follows:

1. Selection of the patient. Absence of contraindications, such as cerebrospinal disease, pyogenic infection at or adjacent to the site of puncture, poor condition of the patient (shock, coma, sepsis, severe hypotension, etc.) obstetrical complication, hypersensitivity to the drug and unfavorable type of patient (neurotic type, those suffering with chronic backache, headache, or migraine).

2. Skin testing for sensitivity.

3. Administration at late first stage or early second stage of labor, when delivery is thought to occur within the following two hours.

4. Observation of all precautionary measures:

a. Barbiturates to counteract possible spinal reaction (particularly where cocaine derivatives are used; Nupercaine is a quinoline derivative).

b. The routine use of ephedrine prior to administration of spinal anesthetic agent partly to guard against preventable fall in blood pressure, and partly as prophylaxis against allergic manifestations, of which postspinal headache may be one.

c. The administration of oxygen in all cases of fetal bradycardia together with the prompt effective treatment of maternal hypotension.

The first two points in our routine are obvious. The selection of time of administration requires elaboration. We have satisfactorily controlled the discomfort of the first stage of labor with effective use of such drugs as morphine, morphine-scopolamine, Demerol, Demerol-scopolamine, barbiturates, and barbiturates in combination with morphine, Demerol, scopolamine, etc. The saddle block anesthesia is reserved for the late first stage or early second stage of labor. Too early administration may impede the progress of labor or necessitate either a repeat injection of the spinal anesthetic agent with all of its concomitant dangers enumerated above, or else resort to other forms of delivery anesthetics. In the latter event, the beneficial advantages of spinal anesthesia is nil and the potential danger too great to justify its use.

We believe the routine use of ephedrine prior to the spinal administration is a wise precaution against preventable blood pressure fall and possible allergic drug reaction. In our preliminary report, ephedrine was only used as dictated by the fall in blood pressure and not prophylactically. In the 67 cases of blood pressure fall exceeding 20 mm. Hg reported in that series, only 13, or 20 per cent required use of ephedrine to restore the pressure to normal range.

There are many advantages of properly used saddle block anesthesia. For the fetus, spinal anesthesia provides maximum protection from two standpoints; (1) pharmacologically, the toxic drug reaction and depression to the baby are absent; (2) mechanically, the trauma to the fetal head is minimized by the elimination of involuntary "bearing down" reflex. The importance of this protection has been emphasized by Masters[6] of George Washington University School of Medicine in the delivery of premature infants.

For the laboring mother, successful saddle block anesthesia provides absolute comfort almost immediately. Due to this comfort the laboring mother is able to take adequate nourishment and fluids and to obtain rest. Furthermore, the presenting part is brought to the outlet by the action of uterine contraction alone, hence the appearance of the presenting part at the outlet indicates complete dilatation and retraction upward of the cervix. The importance of complete retraction of the cervix has been adequately emphasized by Dr. Calkins[7] and needs no comment here.

From the nursing staff's standpoint, the care of the patient is made easier. Only minimum equipment is required, and the perfectly clear mind of the patient makes nursing care simple. Due to the nature of the anesthesia, "last minute" confusion and excitement of imminent delivery are eliminated.

From the obstetrician's standpoint, the advantages are many. It is the anesthetic of choice in cardiac patients, as well as in patients suffering from respiratory diseases. The danger of the complication of aspiration, and the additional narcotizing effect of supplementary delivery anesthesia in patients given heavy predelivery sedation is eliminated. The simplicity of administration makes its use available to all.

The increased incidence of operative deliveries has been cited as a disadvantage. The use of saddle block as a terminal procedure will eliminate most of this objection, as rotation will occur usually before the late first stage or early second stage. That the number of spontaneous deliveries can be increased by utilization of the accessary muscle of expulsion synchronized with uterine contraction has been discussed already. Dieckmann and his associates,[3] in their

series of 719 cases, have also noted no significant increase of operative deliveries. They believe that the late institution of saddle block anesthesia is a factor in producing their low operative incidence.

Summary

Eight hundred seventy-seven attempts at saddle block anesthesia with heavy Nupercaine solution have been analyzed. It provided complete subjective relief of at least one hour's duration in 816 cases, or 93 per cent, and incomplete subjective relief in 53 cases, or 6 per cent. Seven hundred fifty-four patients, or 86 per cent, were delivered under the sole analgesic effect of saddle block anesthesia. In 123 other patients supplementary delivery anesthetic was used to supplement waning spinal effect, for deeper anesthetic to permit operative maneuver and for psychological reasons only. Subjective relief was of one to two hours' duration on the average, but the perineal anesthesia usually exceeded three to four hours' duration. The time of administration was the late first stage or early second stage of labor. The incidence of operative deliveries was found to be low. The untoward effects found were 100 per cent motor weakness, 18 per cent incidence of blood pressure fall exceeding 80 mm. Hg, 14 per cent incidence of postspinal headaches, and a case each illustrating "spinal reaction" and "neurologic complication" (foot drop). There were ten dead babies, of which six were stillbirths and four neonatal deaths. Two neonatal deaths were due to prematurity.

Conclusion

Saddle block anesthesia is the most nearly ideal for obstetrical analgesia and anesthesia if used judiciously by an experienced obstetrician. The maximum safety to the fetus and mother, the dramatic relief of the discomfort of labor and the simplicity of the technique make it attractive for the mother, the nursing staff, and the attending obstetrician. That there are certain potential dangers to the use of this type of anesthesia must be borne in mind at all times. Protracted or permanent neurologic complication may follow spinal anesthesia as well as general anesthesia. Drug reaction may endanger the fetus and the mother. It is, therefore, imperative that the most careful technique be meticulously observed and all precautions taken to guard against any danger. An experienced, qualified obstetrician can minimize the factors contributing to the potential danger. For such individuals, saddle block anesthesia provides the most nearly ideal form of obstetrical analgesic.

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Discussion

DR. JAMES R. BLOSS, Huntington, West Va.—In our own service, which is an entirely private patient one, spinal anesthesia has been practically the only type employed for the past two years.

Metycaine in Ringer's solution has been the drug used. We have been somewhat hesitant about using the hyperbaric solutions and endeavoring to secure the "saddle block." Probably this hesitance has been due to the fact that the results thus far secured have been so satisfactory, in our experience.

It has seemed to us that the very prompt anesthetic effects of metycaine, and the absence of alarming falls in blood pressure, with evidences of the toxic symptoms noted at times when other agents have been employed, make this the more desirable agent.

We do not administer the spinal anesthetic until it is felt that delivery will be effected promptly, usually within an hour. It has appealed to us that more careful attention to analgesia during the first and early second stages has much to do with the successful outcome of the spinal anesthesia. In our experience the intravenous administration of demerol and scopolamine, with a barbiturate given by mouth has proved safe and successful for this purpose.

I am in agreement with Dr. Schmitz that in the hands of an experienced and qualified obstetrician who meticulously observes the most careful technique and takes all precautions to guard against possible but unpredictable complications, such as rapid and extreme fall in blood pressure, etc., this form of obstetric anesthesia provides the most nearly ideal at the present time.

One cannot refrain from re-emphasizing the precautions to be observed and the adherence to a definite routine. We must realize that this procedure is potentially dangerous and that many untoward sequelae may result. This is true of all agents used for obstetric anesthesia when carelessly administered. When carefully administered by qualified obstetricians, the outstanding advantages, to both mother and infant, of this technique for the relief of pain for women in labor justify its employment.

DR. RUSSELL J. MOE, Duluth, Minn.—The results of our experience with saddle block anesthesia in obstetrics using a hyperbaric Nupercaine solution coincide very closely with those reported by Dr. Schmitz. We have found it to be a safe and effective anesthetic agent for delivery.

That there is a need for a safer anesthetic to replace inhalation anesthetics in certain obstetric cases is indicated by a study of maternal deaths due to aspiration pneumonia. A recent one-year maternal mortality study in Minnesota, in which 112 maternal deaths were analyzed, revealed three maternal deaths due to aspiration secondary to an inhalation anesthetic.

In our early experience with Nupercaine saddle block we found it necessary to repeat the puncture in 24.4 per cent of the cases. This was due to the fact that the initial dose was administered too early in the course of labor, particularly in primigravidas.

As a result of too early administration and the necessity of repeat punctures, two facts soon became obvious. First, rotation of the presenting part was necessary in 31 per cent of the cases, and in only one of these was manual rotation possible. The increased irritability of the uterine muscles under saddle block anesthesia makes manual rotation more difficult. However, since using a single intrathecal injection after complete dilatation, the number of necessary rotations has decreased to 6 per cent.

Second, it became apparent that there was an increased incidence of postspinal headaches in the group that had multiple punctures. The single injection group had an incidence of 19 per cent headaches as compared with the essayist's 14 per cent, whereas the multiple injection group had an incidence of 35 per cent. The postspinal puncture headache is a distressing but not a serious complication. We now have two patients who complained of spinal puncture headaches, one of which was classified as severe, who have had subsequent deliveries under spinal anesthesia without headaches.

DR. SAMUEL A. COSGROVE, Jersey City, N. J.—I think it might be well if Dr. Schmitz, in closing the discussion, took pains to offer a definition of exactly what he means by "saddle block." Because, while it is, as several of the discussers have indicated, merely a fanciful name for a low single-shot spinal anesthesia, the term should properly be restricted to that type of low spinal anesthesia which employs a particular agent which assures a more lasting effect than is possible with other agents. It would seem to me that Dr. Bloss is talking about an entirely different procedure when he insists that his Metycaine solution be used within an hour of the delivery of the patient. Now, unless saddle block is definitely defined as above, it does not differ in any sense from the low spinal anesthesia with short-acting agents, such as Novocain. It is the duration of the anesthesia by the particular agent commonly used in saddle block that distinguishes this technique from other techniques. It perhaps justifies our acceptance of a greater incidence of postspinal headache that the Nupercaine ordinarily carries with it as compared to other anesthetics.

DR. CHESTER D. BRADLEY, Newport News, Va.—The impressive work on spinal anesthesia which has been done by Dr. Schmitz and others represents a most wholesome attempt to get away from general anesthesia in obstetrics with its attendant dangers. The hazard of a full stomach is always present and it is doubtful if we are justified in subjecting the parturient woman to the risk of aspiration for the sake of pain relief. So often labor starts after a heavy meal or occasionally a patient will take a snack just before going to the hospital at the urging of solicitous relatives. Even though labor starts as much as three hours after eating, food may remain in the stomach. In a recent case of my own a primipara went into labor three hours after supper. She came into the hospital very soon and had nothing but liquids in the course of labor. During general anesthesia she vomited undigested food which she had eaten twenty-six hours before. On the service of another doctor, the wife of a prominent dentist died on the delivery table under general anesthesia. At autopsy a piece of meat was found obstructing the trachea.

Spinal anesthesia gives a wonderful feeling of safety from this type of complication. Furthermore, one escapes the fetal depression which so often occurs with general anesthesia following heavy sedation of the mother during labor. I confess to a fondness for hearing the newborn baby cry promptly. However, some of us are going to run up against certain difficulties if we attempt to use any form of spinal anesthesia more or less routinely in obstetrics. In the Newport News area where I practice, the public has a deeply rooted phobia against spinal anesthesia. Almost every time I use it I am forced to justify it to the patient and her family. This is not an insuperable obstacle. It could be eradicated by education. However, the headache which occurs so often after spinal anesthesia is a more serious obstacle. I do not let this unpleasant aftereffect deter me from using low spinal anesthesia in selected cases. I use it frequently and I will continue to do so for there are certain types of complicated obstetrical cases in which I feel it is best for both the mother and baby. But I submit that the routine use of any form of spinal anesthesia in private practice is going to give the doctor a lot to explain and justify the postspinal headache to the patient and her family. For this reason I have lately been resorting more and more to pudental block anesthesia for uncomplicated cases.

DR. CHARLES O. McCORMICK, Indianapolis, Ind.—I would like to recommend to this group a form of childbirth pain relief that is free from headache, fall in blood pressure, foot drop and such other handicaps as we have just heard. One that does not involve meticulous technique nor require an expert administrator. In our clinic at Indiana University the administration is performed by the student nurse. The method is simple, extremely safe for both the mother and infant, inexpensive, applicable to practically every woman in labor, and has an efficiency of over 95 per cent. I refer to modified rectal ether analgesia.

DR. CLIFFORD B. LULL, Philadelphia, Pa.—I believe that Dr. Schmitz has brought out two very important findings; one, that the spinal anesthesia must be given by an experienced individual, and second, that the technique must be meticulously carried out. At the present time we are using saddle block in a large proportion of our vaginal deliveries.

I should like to call attention to one or two factors. One, that if the patient is to be delivered within a very short time after the spinal is given it is probably just as well to use a drug which does not last too long. We like to use in cases that are going to be delivered almost immediately, 35 mg. of Metycaine. If the delivery is not imminent and probably will not take place for one or two hours, then we prefer Nupercaine. We have done this because on one occasion we gave a patient Nupercaine and delivered her in about fifteen minutes. Everything went satisfactorily but when the patient went back to her room an hour later, by being moved and changing her posture the anesthesia level rose to the point where she became quite definitely ill. We, therefore, now have the level checked before she leaves the delivery room as we do routinely the blood pressure, pulse rate, and height of the fundus of the uterus. This allows the nurse on the floor to know just where the level was at the time of removal from the operating room and this is tested by her, particularly if she has had Nupercaine used as a drug in the anesthetic. The figures which I quoted in my own paper concerning post-spinal headaches I do not believe to be entirely correct. This is probably due to the fact that the resident neglected to put it on the chart. I can honestly say, however, that we did not become spinal-headache conscious until after we had been using spinal anesthesia in our work for some time. We have not had any that were severe enough to become alarming, and almost all of them were relieved by placing a wasp-girdle on the patient. Sometimes we insert a rubber bladder underneath a scultetus binder and inflate it with air. These patients get almost immediate relief. The results from the use of either spinal or caudal have been so satisfactory in our own clinic that we very seldom resort to general anesthesia. For example, last month, in a total of 132 private patients delivered, there were only 27 of them delivered by the use of general anesthesia.

DR. SCHMITZ (Closing)—Relative to a definition of ''saddle block,'' I think this form of anesthesia received its name from the urologists when they attempted to develop an anesthetic for that section of the perineum which would be placed in the saddle. The entire plan for its use in obstetrics is to prolong the anesthetic effect by making it a hyperbaric solution. One of the important precautions in administering the anesthetic is not having the patient in a sitting position for too long a period, because then the effect is limited to the perineum. Relative to the immediate care of the patient following the delivery, we have instituted what so many obstetricians have described as the care of the patient during the fourth stage of labor. She spends that time in the birth room, with the blood pressure apparatus attached to her arm and the intern does not leave her for an hour or longer until we are assured that there are going to be no complications. Many are using a so-called ''recovery room'' where the patient is under the constant care of nursing and attending staff. We do not have those facilities, so we carry it on in the delivery room.

A TEN-YEAR STUDY OF CESAREAN SECTION IN ROCHESTER AND MONROE COUNTY, 1937 TO 1946*

JAMES K. QUIGLEY, M.D., F.A.C.S., ROCHESTER, N. Y.

WHETHER statistical studies such as this are worth the effort put into them has often been questioned. However, we learn by experience, and reliance upon impressions alone is anything but accurate.

In its study of maternal deaths begun in 1933, the Committee on Maternal Welfare of the Medical Society of the County of Monroe encountered those deaths following cesarean section, and, while many detailed surveys of this operation performed in clinics large and small throughout the country had been made, since few had been published of results in an entire community such as a city, state, or county, it seemed proper that this Committee should attempt to determine just what the experience with cesarean section had been in its own community, the reasons given for its performance, and what was the risk.

Accordingly, under the auspices of this Committee, all cesarean sections done in Rochester and Monroe County during the ten-year period, 1926 to 1935, were studied and published.[1] There were 937 operations in this study and the conclusions drawn were: first, that examination of the hospital records showed that there had been a tremendous increase in the number of indications for the operation and that these indications were not always clearly defined, that in some instances pelvic delivery could probably have been accomplished at no greater risk to the patient; second, that the frequency with which abdominal delivery was resorted to in Rochester was no greater than the average reported by similar studies in the United States, and lower than most; third, that the mortality rate of 2.9 per cent was considerably lower than had been previously estimated, and much below that reported in city-wide surveys made up to this time (1937); fourth, that the low cervical cesarean section showed a much lower mortality rate than the classical operation, and for this reason should be more generally adopted.

Now, at the end of another decade, this survey has been repeated under the same auspices and it is the conclusions of this study of 1,693 cases compared with the first and with others done recently elsewhere that will be presented today.

Eight hospitals are included; however, the two University hospitals, Municipal and Strong Memorial, are grouped as a unit. In addition, there are six other hospitals and they all appear in order as follows: Highland, Park Avenue, Strong Memorial and Municipal (as a unit), Genesee, General, St. Mary's, and Monroe County Infirmary. They will be designated as Hospitals A, B, C, D, E, F, and G. There has been no attempt to separate the ward or staff cases from the private patients; divided statistics would be confusing and would serve no good purpose.

*Presented at the Fifty-Ninth Annual Meeting of the American Association of Obstetricians, Gynecologists and Abdominal Surgeons, Hot Springs, Va., Sept. 9 to 11, 1948.

TABLE I. INCIDENCE

HOSPITAL	TOTAL BIRTHS	CESAREANS	INCIDENCE
A.	11,525	293	1 in 39 or 2.5%
B.	4,672	160	1 in 29 or 3.4%
C.	13,445	260	1 in 51 or 1.9%
D.	9,393	174	1 in 54 or 1.8%
E.	16,543	525	1 in 31 or 3.1%
F.	12,122	268	1 in 45 or 2.2%
G.	835	13	1 in 64 or 1.5%
Total	68,535	1,693	1 in 40 or 2.4%
1926-1935	37,575	937	1 in 40 or 2.4%

The frequency with which resort was made to abdominal delivery varied in the seven hospitals from 3.4 per cent to 1.8 per cent, almost the same as in the previous survey; Hospitals A and B increased slightly while in D and E there was a decrease, and C remained as before. The rate of 1 in 40 or 2.4 per cent was the same as ten years ago.

There has been no increase in the performance of cesarean section in Rochester in ten years and this rate is lower than in those communities and those hospitals shown in the following table:

City of Philadelphia	1931	2.4%	
	1941	2.8%	
City of Syracuse	1947	3.8%	
State of Massachusetts		3.3%	
Cleveland Maternity	1931-1941	6.1%	
Philadelphia Lying-In	1932-1942	5.8%	Private 9.2 Ward 3.6
New Haven Hospital	1935-1944	5.8%	Private 9.6 Ward 3.2
Chicago Lying-in	1938-1942	4.43%	
Boston Lying-in	1934-1943	4.2%	
Methodist, Brooklyn		3.9%	
Garfield Memorial, Wash., D. C.	1947	3.7%	
Good Samaritan, Los Angeles (Annual range of 6.2 to 15.5%)	1925-1944	11.0%	

Indications

Reasons given for this operation were many, in fact 60 were tabulated and are given in Table II. This is an increase of 100 per cent over 1926-1936.

For convenience this list was shortened by grouping and by inclusion of only the most frequent causes. (Table IIA.) The most striking change since the first survey was the increase in the classification, "Cephalopelvic Disproportion," from 3 per cent to 12 per cent. In general, the indications were better defined and substantiated. Contracted pelvis, often simply given as such or divided into various categories, accounted for 24 per cent of the total; cephalopelvic disproportion for 12 per cent; the hemorrhagic states, abruptio and placenta previa, 14 per cent. In 267, or 15 per cent, previous section was given as the indication; this did not include those cases where the reason for the first section, contracted pelvis or other obstructive cause, was present at the time of the subsequent section. The group, elderly primiparas, was subdivided equally between those operated upon before the onset of labor and those in labor, many ofter a good trial.

Two patients were operated upon because of hydrocephalus and one was done at the time of appendectomy for suppurative appendicitis and peritonitis. Both are questionable reasons. The rate for eclampsia as an

TABLE II. INDICATIONS

	HOSPITAL							
	A	B	C	D	E	F	G	TOTAL
Contracted pelvis	37	31	41	24	23	29	3	188
Justo-minor pelvis	1	9	7	6	43	4		70
Flat pelvis	22		2	6	28	11		69
Funnel pelvis	4	5	6	13	34	9		71
Rachitic pelvis			1					1
Kyphotic pelvis						1		1
Kyphosis and scoliosis					1			1
Spondylolisthetic pelvis					2			2
"Tilted pelvis"					2			2
Fractured pelvis					3			3
Osteoma of pelvis			1					1
Disproportion (fetal-pelvic)	79	19	1	5	54	48		206
Ankylosis of hips					2			2
Deformed vagina					2			2
Uterine myoma	2		12	5	9	9		37
Ovarian cyst			3	1	2	2		8
Atresia of cervix			4					4
Stenosis of cervix after amputation		4						4
Previous cesarean	38	8	36	34	91	58	2	267
Abruptio placentae	14	6	22	10	29	17	1	99
Placenta previa	17	19	9	21	58	22	2	148
Toxemia	14	7	11	6	42	17		97
Eclampsia	2	1		1	3			7
Heart disease	5	2	14	1	6			28
Pulmonary tuberculosis	1	1	16	6	7	1		32
Diabetes	1		2	1	2			6
Nephritis			5	2				7
Previous pelvic repair	7	1	7	7	7	5	1	35
Previous hard labor			2		1	1		4
Previous hard labor with stillbirths	1	1	7	1	9			19
Previous perforation of uterus			1					1
Elderly primipara, no labor		1	6	2	9	6		24
Elderly primipara after trial labor	5		7	1	12			25
Ruptured uterus	2			1	3			6
Rectovaginal fistula	1	1						2
"Soft part dystocia"		5		1	3			9
Cervical dystocia	7		19	3	2	16		47
Cancer of cervix			1			1		2
Uterine inertia		1		3		4		8
Contraction ring dystocia		1	1		2			4
Trial labor	17	7		8	16	1	1	50
Failed forceps					2	1		3
Transverse position		2	3	4	3	1		13
Other malpresentation	3	1	1	1	3	1		10
Poliomyelitis			2		2			4
Pyelonephritis					1			1
Hydronephrosis					1			1
Cerebral hemorrhage					1			1
Subarachnoid hemorrhage					1			1
Brain tumor			1					1
Purpura			1					1
Chronic atelectasis					1			1
Vasa brevia			1					1
Rh disturbance			1		4			5
Fetal distress	4	1	2			2		9
Prolapsed cord	1					1		2
Ruptured appendix						1		1
Not specified	8	24	3					35
Epilepsy							1	1
Hydrocephalus		1					1	2
Bicornate uterus							1	1

indication was less than ten years ago, 7 operations, with a mortality of 28.6 per cent; this alone is enough to condemn it. In addition to these cases of eclampsia, the only mortality in 525 sections in Hospital E was from eclampsia in an elderly primipara operated upon for toxemia who developed eclampsia postoperatively.

TABLE IIA.—INDICATIONS

	A	B	C	D	E	F	G	TOTAL	RATE (PER CENT)
Contracted pelvis, all forms	64	45	59	49	136	54	3	410	24
Cephalopelvic disproportion	79	19	1	5	54	48	0	206	12
Previous cesarean section	38	8	36	34	91	58	2	267	15
Placenta previa	17	19	9	21	58	22	2	148	8.7
Abruptio placentae	14	6	22	10	29	17	1	99	5.2
Toxemia of pregnancy	14	7	11	6	42	17	0	97	5.1
Heart disease	5	2	14	1	6	0	0	28	1.7
Pulmonary tuberculosis	1	1	16	6	7	1	0	32	1.8
Malpresentation	3	3	4	5	6	2	0	23	1.3
Cervical dystocia	7	0	19	3	2	16	0	47	2.7
Trial labor	17	7	0	8	16	1	1	50	2.9
Elderly primiparae	5	0	13	3	21	6	0	48	2.8
All others	21	19	53	23	57	26	4	203	12.0
Not specified	8	24	3	0	0	0	0	35	1.9

Type of Operation

In the survey ten years ago there were no extraperitoneal operations and the classical section was done almost four times as frequently as the low cervical. In the second ten-year period the extraperitoneal section was done thirty times and the number of classical and low cervical sections were practically equal. In Hospital E the increase in the low flap operation was more striking:

1926-1936	41 per cent low flap operations
1937-1941	60 per cent low flap operations
1942-1946	88 per cent low flap operations

This increase in the frequency of the low cervical operation is not merely limited to Rochester. The New Haven Hospital, Chicago Lying-in, the Margaret Hague, and the Women's of New York all report many more low flap operations than classical. At Boston City Hospital, 91 per cent of the 961 sections done between 1936 and 1946 were of the low cervical type.

TABLE III. TYPE OF OPERATION

HOSPITAL	CLASSICAL		LOW CERVICAL		CESAREAN HYSTERECTOMY		EXTRA-PERITONEAL		NOT SPECIFIED	
	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT
A	132	45	140	47	4	1.3	17	5.7	0	
B	103	64	31	19	0		0		26	16
C	171	65	65	25	24	9.2	0			
D	141	81	23	13	8	4.6	2	1.1		
E	106	20	406	77	6	1.1	7	1.2		
F	133	49	115	42	16	6.0	4	1.5		
G	7	54	6	46	0		0			
	793	46.8	786	46.3	58	3.4	30	1.7	26	1.6

Morbidity

The index used was that of the American Committee on Maternal Welfare, viz., a temperature of 100.2° F. on two successive days not including the

day of operation. This criterion is probably the best single indication of operative complication. However, it does include causes unrelated to the operation such as urinary infection, mastitis, respiratory infections, and, conversely, complications of serious import to the patient may not be manifested by a rise in temperature and may still be considered morbid or even fatal. Illustrations are hemorrhage, atelectasis, dehiscence of the abdominal wound, and the toxic states.

TABLE IV. MORBIDITY

HOSPITAL	CESAREAN SECTIONS	NO. MORBID	RATE (PER CENT)	RATE 1926 TO 1935 (PER CENT)
A	293	107	36	35
B	86*	37	43	50
C	260	100	38	38
D	174	60	34	54
E	525	229	43	34
F	268	66	24	35
G	13	8	61	44
	1,619	607	37	38

Data on morbidity available only for 1942-1946. Adhering to the above index, however, the morbidity for all hospitals was 37 per cent with a range of 24 to 61 per cent.

Experience Elsewhere.—

Boston Lying-in	21.1 per cent
Chicago Lying-in	43.8 per cent
Cleveland Maternity	45 per cent
Methodist Episcopal, Brooklyn	53.1 per cent
City Survey, New Orleans	61.3 per cent

Conditions Influencing the Morbidity Rate.—

Length of labor, rupture of the membranes, and vaginal examinations are three factors considered by most obstetricians in deciding for or against operation.

TABLE V. FACTORS INFLUENCING MORBIDITY

HOSPITAL	PATIENTS IN LABOR	EXAMINED VAGINALLY	MEMBRANES RUPTURED
A	116	14	44
B	43	12	12
C	48	42	37
D	33	19	25
E	220	67	85
F	99	57	59
G	1	3	0
Total	560 33%	214 12%	262 18%
	276 morbid or 47%	124 morbid or 58%	141 morbid or 53%

Many of the 560 patients in labor underwent long tests, real trial labors; 245 had labors of over 24 hours for an average of 39 hours, 36 minutes each. Most women examined vaginally were examined only once, a few twice, and two three times. Two hundred sixty-two cases, or 18 per cent, had ruptured membranes before operation. Time elapsing after rupture of the membranes was over twenty-four hours in many cases and in one five days. There was a rather close correlation of these three factors to the morbidity as expressed in febrile reaction, though some patients sectioned after long labors had no postoperative fever, and, conversely, many were febrile following elective operations where the membranes were intact and there was no vaginal exploration.

Relation of Patients in Labor to Morbidity.—

Of 560 in labor, 276 were morbid, 47 per cent as against a general morbidity rate of 37 per cent. Two hundred fourteen women were examined vaginally and 124, or 58 per cent, were morbid. In 262 the membranes had ruptured before operation and 141 were morbid, a rate of 53 per cent against 37 per cent.

Sterilization

In 254 operations the patients were sterilized, 15 per cent of the total. Most of these were done by the Madlener technique. In Hospital F the sterilizations were limited to those cases requiring hysterectomy.

Additional Surgical Procedures at the Time of Cesarean Section

One appendectomy was done for suppurative appendicitis. Myomectomy for fibroids was performed on fifteen patients, and one patient was sectioned at term because of myomectomy in her third month. There was one case of placenta accreta for which hysterectomy was done.

Repeat Operations

There were 442 repeat sections. The indication given in 267 cases was simply previous cesarean section. This leaves a balance of 175 where the reason for the first section was still present such as contracted pelvis or healed pulmonary tuberculosis or previous pelvic repair. Of course some of the patients in this stury were subsequently delivered through the pelvis, just how many was not determined.

TABLE VI. NUMBER OPERATED UPON BY OBSTETRICIANS

HOSPITAL	TOTAL CESAREANS	OPERATED UPON BY OBSTET.	NUMBER OF OBSTET.	OPERATED UPON BY SURGEONS	NUMBER OF SURGEONS	OPERATED UPON BY GENERAL PRACTITIONER	NUMBER OF GENERAL PRACTITIONERS
A	293	286 97%	15	7	5	0	0
B	140	115 82%	10	25	5	0	0
C	260	260 100%	18	0	0	0	0
D	174	161 91%	12	13	5	0	0
E	525	517 98%	15	3	2	5	2
F	268	237 88%	5	31	9	0	0
G	13	12 92%	5	1	1	0	0
	1,673	1,589 95%	80*	80 4.7%	27	5	2

*Thirty-four different obstetricians operated.

Of 1,673 cesarean sections, 1,589, or 95 per cent, were done by obstetrical specialists of whom there were thirty-four, all occupying positions on obstetrical staffs and practically all of them limiting their practice to obstetrics. Fifteen are diplomates of the American Board of Obstetrics and Gynecology. There were five patients operated upon in the early years of this series by two general practitioners assisted by staff obstetricians. Eighty operations, or nearly 5 per cent of the total, were done by twenty-seven general surgeons.

Fetal Mortality

Obstetrical and other causes for fetal mortality were: abruptio placentae 41, placenta previa 23, eclampsia and toxemia 12, asphyxia and atelectasis 8, erythroblastosis 3, congenital heart disease 3, other congenital abnormalities 4, pneumonia in infant 1, cerebral hemorrhage 1, unknown 35.

TABLE VII. STILLBIRTHS AND NEONATAL DEATHS

Hospital A	22
B	12
C	28
D	10
E	40
F	20
G	2
	134 or 7.9 per cent uncorrected*

*Including many premature and some nonviable infants.

A fetal mortality rate of 7.9 per cent seems high for an operation frequently done in the interest of the child. Forty-one deaths resulted in the cases of abruptio placentae, which carries a high infant mortality rate under any treatment. These were almost all stillbirths. Placenta previa accounted for 23 and eclampsia and toxemia for 12. These three causes took 76 fetal lives, about 60 per cent of the 134 lost. Asphyxia and atelectasis were responsible for eight, a not unusual proportion. There were only six congenital abnormalities such as spina bifida, congenital heart disease, etc. Earlier diagnosis and treatment of premature separation and placenta previa would help to lower the infant death rate in cesarean section. Only assistants properly trained in resuscitation of the newborn should be entrusted with this detail in the operating room.

Maternal Mortality

The portion of this survey dealing with maternal mortality is the most interesting and encouraging feature of the study, for all hospitals showed an improvement and the rate for the entire city was only one-third that of ten years ago. Sixteen deaths in 1,693 operations gives a rate of 0.94 per cent which is very low for this type of survey, though a few individual hospitals have reported several hundred cesarean sections with a rate of less than 1 per cent. In this series the rate per hospital varied from 7.69 per cent, where 1 death occurred in 13 operations, to 0.19 per cent in another hospital, where one patient died in 525 cesareans.

TABLE VIII. MATERNAL MORTALITY

HOSPITAL	CESAREANS	DEATHS	RATE (PER CENT)	RATE 1926-1935 SURVEY (PER CENT)
A	293	2	0.68	2.1
B	160	5	3.12	7.4
C	260	2	0.76	2.5
D	174	2	1.14	5.1
E	525	1	0.19	1.1
F	268	3	1.12	4.2
G	13	1	7.69	11.0
Total	1,693	16	0.94	2.9

Ten to fifteen years ago there was an impression that the death rate for abdominal delivery the country over was at least 5 per cent, though many clinics at this time had reported lower rates.

Table IX shows the improvement in other communities and the present low rates in some of the largest lying-in hospitals.

TABLE IX. AN IMPROVED CESAREAN SECTION MORTALITY RATE

HOSPITAL	YEAR	NO. SECTIONS	PER CENT
Philadelphia entire city	1931		6.1
	1935		4.6
	1940		1.8
State of Mass.		11,030	2.4
Philadelphia Lying-In	1932-1937	665	2.55
	1937-1942	657	1.37
Boston Lying-in	1934-1938	912	1.9
	1939-1943	975	0.7
Chicago Lying-in	1931-1944	1,790	0.61
	1942-1944	317	0.00
Methodist, Brooklyn	1920-1938	1,066	3.18
Johns Hopkins	1922-1931	386	4.4
	1932-1941	750	1.7
Cleveland Maternity	1931-1941	1,317	1.7
Rochester General	1938-1948	604	0.00
Five United States Maternities since 1931 (Collected by Dieckmann)		6,335	1.46

TABLE X. MORTALITY OF TYPES OF CESAREAN SECTION, ROCHESTER

	OPERATIONS	DEATHS	RATE (PER CENT)	RATE 1926-1935 (PER CENT)
Classical	793	11	1.38	3.34
Low cervical	786	2	0.25	1.02
Cesarean hysterectomy	58	1	1.72	8.69
Peritoneal exclusion	30	2	6.66	
Not reported	26			

The rate for the low cervical operation in the first ten-year study in Rochester was one-third that of the classical operation, and in the second series less than one-fifth, in spite of the fact that in many institutions the low flap cesarean is performed almost entirely upon patients after trial labors and the classical operation is reserved for the elective cases. Further proof of desirability of the low cervical operation because of its lower risk is shown in the following table collected by Dieckmann:

TABLE XI. MORTALITY OF TYPES OF CESAREAN SECTION

	CLASSICAL		LOW CERVICAL	
HOSPITAL	NO.	MORTALITY (PER CENT)	NO.	MORTALITY (PER CENT)
Margaret Hague	117	6.8	1,261	1.03
Boston Lying-in	372	2.1	168	4.20
Chicago Lying-in	22	18.1	1,618	0.38
Women's Hospital, N. Y.	235	4.3	620	2.10
Total	746	4.0	3,667	1.07
Collected by F. Irving	3,334	6.7	2,006	1.85

For at least twenty years the writer has urged the more general adoption of the low flap technique in all cesarean sections[2] and the observation made in the first ten-year report in Rochester is here repeated: "One cannot escape the conviction that the mortality rate for the low cervical cesarean section or laparotrachelotomy is one-half or even less than one-half that of the classic operation—it must therefore be safer and should be more generally adopted. In addition to many other advantages there is notably less liability for rupture of the uterus in subsequent pregnancies."

TABLE XII. FATALITIES

HOSPITAL	YEAR	INDICATION	TYPE	LABOR (HOURS)	VAGINAL EXAMINATION	MEMBRANES RUPTURED	AUTOPSY	CAUSE OF DEATH	AGE	PARA	DAYS POSTPARTUM
A	1941	Desire of patient	Hurst	0	1	24	0	Sepsis	32	ii	14
	1940	Eclampsia	Classical	0	0	0	0	Eclampsia	22	0	2
B	1938	Face presentation fibroids	Classical	0	0	0	0	Peritonitis	42	0	16
	1939	Disproportion	Classical	30	0	0	0	Pul. embolus	28	0	16
	1940	Transverse position	Classical	30	2	Artificial	Yes	Peritonitis	37	0	42
	1942	Contracted pelvis	Classical	37	2	0	0	Pul. embolus	26	ii	4
	1942	Disproportion	Classical	48	0	0	0	Peritonitis	21	0	19
C	1941	Previous repair	Low cervical	48	1	0	0	P.P. hemorrhage	35	iii	1
	1944	Rh, heart disease	Classical	0	0	3	Yes	Rh. ht. dis.	25	0	27
D	1941	Eclampsia	Low cervical	0	0	0	Yes	Thrombosis carotid artery	36	0	10
	1943	Placenta previa	Classical	0	1	0	Yes	Peritonitis	42	0	7
E	1938	Toxemia	Classical	0	0	0	0	Eclampsia	38	0	8 hr.
F	1937	Disproportion	Classical	0	0	0	0	P.P. hemorrhage	31	0	6 hr.
	1941	Justo minor	Classical	0	0	0	Yes	Peritonitis	32	0	4
	1946	Abruptio	Cesarean hysterectomy	0	0	0	0	Peritonitis and heart disease	32	ii	6
G	1942	Disproportion	Attempted Waters' operation	36	2	15	Yes	Peritonitis	20	0	13

TABLE XIII. MORTALITY OF VARIOUS CONDITIONS TREATED BY CESAREAN SECTION

	NUMBER	DEATHS	RATE (PER CENT)
Abruptio placentae	99	1	1.00
Placentia previa	148	1	0.67
Eclampsia	7	2	28.60
Heart disease	28	1	3.50
Toxemia	97	1	1.00
Pulmonary tuberculosis	32	0	0.00
Contracted pelvis and disproportion	616	5	0.81

Causes of Death.—

Peritonitis	7
Sepsis	1
Postpartum hemorrhage	2
Eclampsia	2
Pulmonary embolism	2
Rheumatic heart disease	1
Thrombosis carotid artery in an eclamptic	1

While it is often claimed that cesarean section is blamed for deaths due to the condition requiring operation, 11, or 68 per cent, of the deaths in this series were attributable to the operation.

One hundred forty-eight cases of placenta previa with one death and a single fatality in 99 cases of abruptio placentae is a low rate indeed, while 28.6 per cent mortality for eclampsia treated by cesarean section simply confirms the impression that these patients are not good risks for this method of delivery.

Conclusions

Two surveys of ten years each on all cesarean sections performed in all the hospitals, large and small, in a community of 400,000 showed a low incidence of this operation in both surveys. The mortality rate was low; for the second period only one-third that of ten years ago, viz., 0.94 per cent, and this is the lowest rate ever reported for a community survey.

Forty-six per cent of all operations were of the low flap variety and the mortality of this type of operation was less than one-fifth that of the classical operation. There were no deaths from peritonitis or sepsis in this group; the two deaths following the low flap operation were due one to hemorrhage and the other to thrombosis of the carotid artery in an eclamptic.

Factors which probably contributed to a mortality rate one-third that of the first survey ten years ago were: First, 95 per cent of the operations were done by obstetrical specialists. Consultation is compulsory in all complicated obstetrical cases in all hospitals. Second, chemotherapy and penicillin were employed. Third, the value of early and sufficient transfusions was recognized. Fourth, all cases received better maternal care. All these were reflected in a low general maternal mortality rate—6 per 10,000 in 1944, or 2.8 per 1,000 births, 1933 to 1944, for the county.

If 1,693 sections in hospitals large and small have a mortality rate of approximately 1 per cent, this rate should not be exceeded by well-staffed maternities. It is more important to consider the contraindications for the operation than the indications.

References

1. Quigley, James K.: New York State J. Med. 40: 699, 1940.
2. Quigley, James K.: New York State J. Med. 25: 49, 1925.

Discussion

DR. LOUIS E. PHANEUF, Boston, Mass.—Dr. Quigley's second survey of cesarean sections for a ten-year period in Rochester and Monroe County is a valuable contribution to the subject. This second survey shows the adoption of the extraperitoneal cesarean section,

and a high increase in the number of low or cervical cesarean sections with improved results. The improvement in maternal mortality is to be commended as this is very low. We must bear in mind that the mortality of cesarean section is governed, to a certain extent, by the type of patient on whom the operation is done. It is always higher in the neglected case than it is in the clean case, in which there have been no labor nor examinations.

Ninety-nine cases of abruptio placentae with but one death, and one hundred forty-eight cases of placenta previa with but one death is indeed an excellent record.

In order to discuss Dr. Quigley's paper, I have looked up my personal cesarean sections from Jan. 1, 1938, to Jan. 1, 1948, and find that during this period of ten years I have done one hundred ninety-six operations, divided as follows: transverse cervical cesarean sections, 162; extraperitoneal cesarean sections, 12; peritoneal exclusion cesarean sections, 4; low classical cesarean sections, 8; and Porro cesarean sections, 10. In this group there were 69 cesarean sections, or 30.1 per cent, which were repeat operations, and 127 cesarean sections in which the indication was other than a repeat operation—12.7 operations per year.

The indications for the classical cesarean sections, which I seldom do, were: Uterus adherent to the abdominal incision from previous sections, so that the uterus was incised without entering the peritoneal cavity, four cases; and lower segment not formed in premature delivery, four cases, or a total of eight classical cesarean sections in the group.

The maternal mortality was 4 in 196 cases, or 2 per cent.

CASE 1, June 20, 1939.—Died of shock and hemorrhage after a Latzko extraperitoneal operation.

CASE 2, Aug. 25, 1939.—Died of embolism on the hospital steps, as she was going home, on the twelfth postoperative day, following a transverse cervical cesarean section.

CASE 3, Jan. 30, 1941.—Died after a transverse cervical cesarean section; the autopsy showed: "General plastic peritonitis, primary in the left tube and ovary. Uterus clean and healing."

CASE 4, June 5, 1941.—Died of hemorrhage from a central placenta previa, following a classical cesarean section.

The fetal mortality was 9 in 196, or 4.5 per cent. Death was ascribed to the following causes: stillborn, 3; purpura hemorrhagica, 1; monster, 1; and prematurity, 4.

DR. FREDERICK H. FALLS, Chicago, Ill.—The discussion of all of the papers on cesarean section at this meeting has been pointed at the difference between the low cervical and classical type of cesarean section stressing the difference in mortality betwen the two operations. The outcome in fatal cases, in my opinion, is due not to whether a low cervical or a classical operation is done, but to who does the operation, and why it is done, and the condition of the patient, when the indication for the cesarean section arises. There is only one way that one can determine which is the better operation and that is for the same man to alternate these operations in consecutive cases. We have been doing this for a number of years, and have approximately 250 cases. As far as we can see, whether you make the incision in the uterine musculature within an inch of the symphysis pubis, or within 3 inches of the symphysis pubis, it does not make much difference. It sometimes happens that cesarean section is the best way out of a desperate situation. I remember a patient with a severe frontal sinus infection which had been drained. She had been transferred to the contagious hospital at the University of Iowa because erysipelas developed in the frontal wound, and when I first saw her she was in the erysipelas ward and had a temperature of 104° F. and had had four eclamptic convulsions. It was hardly a case that one would want to elect for cesarean section. Under the circumstances I felt that the baby had some chance, the mother almost none. I heard the heart tones and noted that the woman was 32 weeks pregnant. I took her down to the basement (they did not have an operating room) where they did the postmortem examinations, put her on the table, opened the abdomen, took out the live baby and decided I might as

well take out the uterus so she would not die of puerperal sepsis even if she did develop streptococcal peritonitis. The woman did not die and the baby did not die. I took a chance on spoiling my statistics for cesarean section. If I had done either classical or low cervical and if the woman had died the case would have been one against whatever operation I had performed, which would have been manifestly unfair to that operation. It seems to me in all of our statistics of this kind we must determine and take into consideration whether the mortality can be proved to be due to the operation, or whether the mortality is due to the condition for which the operation is undertaken.

DR. NICHOLSON J. EASTMAN, Baltimore, Md.—The statistical analysis of several hundred case histories, even in one's own hospital, is quite an undertaking, and Dr. Quigley has presented a searching statistical analysis of 1,693 cases from seven different hospitals, and simply on the basis of the labor entailed he is to be complimented on the vast amount of information this observation brings forth. I will limit my remarks to one topic; namely, one of the important frequent indications for cesarean section, cephalopelvic disproportion.

In this study, 206, or about one-eighth of the cesarean sections, were done because of cephalopelvic disproportion. In Hospital A, one-fourth of the sections were on the basis of cephalopelvic disproportion; in Dr. Hennessy's series it was the second, and in Dr. Lull's, it was the most frequent indication. Cephalopelvic disproportion is an imposing term, it is widely accepted as a legitimate reason for cesarean section and, of course, is deply entrenched in our literature. Nevertheless, I should like to raise some questions as to its validity.

If we go back to Dr. Quigley's report, in Hospital A, some 79 cesarean sections were done in the course of several hundred for cephalopelvic disproportion, one-fourth for that reason; in Hospital C in the course of 160 only one was done because of cephalopelvic disproportion. This shows a lack of uniformity in the use of this term in the two hospitals and, by the same token, a difference in the way of thinking about cephalopelvic disproportion. Another observation that is pertinent to the question may be based on Dr. Quigley's list of indications. Whereas there are 206 cases of cephalopelvic disproportion, there are also some 400 cases of contraction of the pelvis.

Now, in general, the term cephalopelvic disproportion carries with it the connotation of contracted pelvis, and the question comes up as to why it is necessary to have this group of cephalopelvic disproportion, plus the group of contracted pelves. There are several explanations that might make this plausible. You may have cephalopelvic disproportion without contracted pelvis because of an excessive size child. This is seen in less than 1 per cent of cases and does not loom large. Disproportion may be due to an occiput posterior presentation, giving larger diameters of the head to go through the pelvis. This may account for some of these cases without a contracted pelvis. Nevertheless, if this be true I should think it would lead to clarity to regard occiput posterior as the indication. In some cases of cephalopelvic disproportion, the pelvis may be slightly small and the baby slightly large and it is difficult to tell just which of these is the predominating cause of dystocia. We all know that such cases occur not infrequently but I doubt if they occur as often as these figures would indicate.

There is still another explanation which is probably the right one, namely, that the cases designated as cephalopelvic disproportion were instances of uterine inertia. The patient enters the hospital with the fetal head high; the cervix does not dilate, and after sixteen to eighteen hours, things come to a standstill, and it is decided that something must be wrong. Since the head does not come down, the dystocia is assigned to cephalopelvic disproportion. Every year we see twelve or fifteen cases in which a baby has been previously delivered elsewhere by cesarean section because of cephalopelvic disproportion. We have studied these pelves by x-ray and in most instances the pelvis has been perfectly normal, and in many decidedly large. In quite a number we have delivered these women vaginally of infants much larger than the previous section baby. Hence, I am a little skeptical about this term, believe it is abused and that its use is often due to failure to recognize uterine inertia rather than any actual lack of space.

DR. LEWIS F. MC LEAN, Buffalo, N. Y.—Allow me to review briefly our cesarean section record for the past ten years at the Millard Fillmore Hospital, Buffalo, New York.

Our active staff consists of fourten members, eight of whom have a diplomate status. The remainder are junior members who limit their practice to obstetrics and gynecology and expect to qualify for their boards. This nucleus supervises the work of about one hundred practitioners who have courtesy privileges in obstetrics.

The accompanying table shows the record of sections for the ten years, 1937 to 1947, inclusive. The section incidence is relatively high, varying from 6.2 per cent to 10.8 per cent. Between the years 1937 to 1947, inclusive, the section mortality rate varied from 4.3 per cent to 1.1 per cent. In the years 1946 and 1947 it dropped to zero.

TABLE I

YEAR	DELIVERIES	SECTIONS	PER CENT SECTIONS	SECTION MATERNAL MORTALITY RATE (PER CENT)
1937	1426	154	10.8	1.8
1938	1725	139	8.0	2.5
1939	1441	132	9.16	4.0
1940	1866	119	6.3	4.3
1941	2265	139	6.2	1.4
1942	3067	193	6.3	1.0
1943	3773	302	8.0	2.6
1944	3095	256	8.2	1.1
1945	3123	241	7.6	0.8
1946	3578	308	8.1	0
1947	4049	334	8.2	0

Our last cesarean death occurred in November, 1945. Since that time, in a period of two years and ten months, nearly 900 sections have been performed with no maternal deaths.

This marked reduction has paralleled a similar reduction in the obstetrical maternal mortality. From the years 1940 to 1944, inclusive, the maternal mortality ranged from 0.13 per cent to 0.4 per cent. In 1946, it dropped to 0.058 and in 1947 to 0.049 per cent. This marked drop can be ascribed in part to better blood bank facilities, increased resident staff, antibiotics, etc. We believe, however, that the change was mainly due to the institution of an obstetric recovery room in September, 1945. A review of our maternal deaths disclosed that many of them occurred in the several hours following delivery, and apparently could have been prevented by vigilant supervision and vigorous treatment.

We placed eight beds in two unused rooms in the delivery wing. Every postpartum patient remains there for eight hours following delivery. A graduate nurse is in constant attendance and notes the pulse, blood pressure, amount of flow, condition of the fundus, etc., and records the data on a special chart.

If any abnormal signs (that is, abnormal bleeding) occur, the Resident is called and undertakes remedial measures at once. These may include exploration of the birth canal, suturing, ligation of bleeding vessels, packing, transfusion, etc. A supply of Type IV O, Rh-negative blood with Witebsky anti-A and anti-B substance is available on the delivery floor at all times and can be given immediately. We do not give plasma or saline infusions in hemorrhage cases. Blood is always immediately available and is always given.

We believe that the above measures have made cesarean section a safe procedure in our hospital. Accordingly, we do not hesitate to employ it when we think that the well-being of mother and child demand its use.

OVOGENESIS IN THE ADULT HUMAN OVARY*

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IT HAS been taught for many years that the primordial ova are all formed by the time of birth. The number in each ovary has been stated to vary between 100,000 and 400,000. The discrepancy in these numbers is due perhaps, as Simkins has so well pointed out, to the fact that the methods used in making these counts were only approximate ones. Evans and Swezy, some twenty years ago, became interested in ovogenesis in mammals and they showed conclusively that ovogenesis in the rat, guinea pig, dog, cat, and man occurs throughout the whole active period of the estrous cycle. They presented some material from the human being and came to somewhat similar conclusions as regards the menstrual cycle. In the rat, guinea pig, and dog, the follicular cycle coincides normally with the estrous cycle. They felt that in man the follicular cycle had no necessary relation to the menstrual cycle, ovulation taking place at any time during the menstrual cycle. They claimed that the ova arrived from proliferations of the germinal epithelium in the form of invaginating cords forming groups of epithelial cells which cut off from the epithelium and passed through the tunica albuginea. These cell groups pass into the cortex, enlarge, and some develop into sex cells, the remaining epithelial cells in the group forming the living follicular cells.

Extensive degeneration of the sex cells is a normal process in each cycle. It occurs at all periods, but is at its maximum at the anestrum or proestrum in mammals. Degeneration is seen both in cells and in the ovum. In man there is a somewhat similar relationship of ovogenesis to the ovulation cycle which seems to characterize the mammals generally. Evans and Swezy feel that ovulation in man occurs at approximate intervals of 28 days, but this rhythm bears no exact or invariable relationship to the menstrual cycle. The concept that in the mammals the ova are all formed before birth and remain quiescent until cycle maturity has no foundation in fact. On the contrary, all of the ova of adult life are new formations and are being constantly produced and are constantly being destroyed. It was always our impression that ovulation in the human being in a 28-day cycle occurred, usually, between the fourteenth and eighteenth days. We felt this was clearly shown by the work of Allen, Pratt, Newell, and Bland in 1930.

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Simkins, in 1932, studied the maturation of the human ovum. He, as well as Swezy and Evans, has described minute changes in the maturation of the ovum up to birth. After birth, these changes do not occur and are, therefore, of no special interest in this review of a study of the more mature ovary. In adult life, the only change as regards maturation is the extrusion of the first and second polar bodies at the time of ovulation, a rearrangement of the Golgi apparatus, changes in the yolk granules and mitochondria.

Simkins shows an interesting table concerning the number of ova present at birth to 14 years. He divides the undeveloped follicles into two groups, the primordial follicles and the primary follicles. He described a primordial follicle as an ovum which is inconstantly and incompletely surrounded by flat and ellipsoidal cells and the primary follicle as one which is completely and constantly surrounded by rounded cells. The primordial follicles have an average diameter of 30 microns and the primary follicles of 50 microns. At birth he estimates 115 primordial follicles in the low-power field with only three primary. At 14 years of age, the primordial follicles are reduced to the low average of three to a low-power field and the primary follicles remain the same.

TABLE I. (SIMKINS)

AGE	PRIMORDIAL FOLLICLES IN LOW-POWER FIELD	PRIMARY FOLLICLES IN LOW-POWER FIELD	ESTIMATED NUMBER IN ONE OVARY
At birth	115	3	143,000
5 months postpartum	78	4	112,000
6 months postpartum	48	3	86,000
3 years	41	4	79,000
7 years	16	4	48,000
8 years	18	3	23,760
9 years	9	4	18,000
14 years	3	3	10,500

In this table, Simkins shows the marked diminution of follicles from birth to 14 years, inclusive. This diminution is due chiefly to the primordial follicles, the primary follicles being comparatively few from the beginning. For Simkins' definition of primordial and primary follicles see text.

The chief difference in the work of Evans and Swezy and Simkins is that they disagree as to the origin of the new ova in the adult ovary. Simkins feels that there is no activity of the germinal epithelium after birth, that the tunica albuginea is inactive and there are no tubes or cord cells ramifying into the stroma of the ovary carrying with them new gonocytes throughout the period of cycle fertility. He feels that new ova arise from the cells of a neogenic zone which are not to be considered as germ cells, but somatic cells induced to grow into germ cells by the follicular stimulating hormone of the anterior lobe of the hypophysis. This supposition brings our attention to the so-called cortex of the ovary which, heretofore, has not been recognized as a parenchymatous part of the organ and usually is described as entirely connective tissue. We shall elaborate further concerning the appearance and structure of the cortex in reviewing our own observations.

In studying the work of these investigators, this rather controversial idea as to direct origin of the germ cells was most interesting. We think it rather amazing and somewhat disturbing that such a subject, which might suggest definite changes in therapy in treatment of certain clinical conditions—chiefly, sterility, amenorrhea and the anovulatory cycle, has not been discussed among the gynecologists in relationship concerning the facts in these two very important

contributions. No adequate work has been done with the view of presenting further evidence of the presence of the admitted newly developing ova in adult life. It is also remarkable that in the latest editions of textbooks on gynecology and obstetrics, in discussing the histology of the ovary, there has been no noticeable change made concerning the long-accepted older view of nonproduction of new ova after birth. Novak mentions the new subject in passing, but feels that further investigation is necessary for definite conclusions. Hamblen also refers to this work in his monograph. In 1934, in his textbook on histology, Cowdry mentions the contentions of Evans and Swezy in some detail and apparently accepts them as well in man as in other mammals.

For some time we have thought it might be of interest to review some additional human material in the attempt to determine what this situation might mean to us. Accordingly, we selected at random from recent files of our gynecological service, which have accumulated for many years, sections of ovaries from operative material which have been removed from patients in various decades of life, about 800 in number. The more recent files were considered because of better staining and better fixation, the routine being that the specimens are placed in 10 per cent formalin in the operating room. Fixation, therefore, in most cases was adequate and particularly since the very detailed minutiae of the study of maturation of the ovum before birth were not a part of this study, we feel that our material is fairly representative. These sections were studied in connection with their clinical history in which the age and the menstrual history could be obtained in the vast majority of instances. In addition to reviewing the character of the ovary from late fetal life through to adult life by means of some good autopsy material, we wished to study particularly the character of the germinal epithelium, the tunica albuginea, the cortex, the type and number of follicles present, as well as the picture of the corpus luteum.

Material

The changes in the germinal epithelium and the tunica when active presented themselves very strikingly and without going into great detail concerning these changes, we shall rather point them out in the descriptions in the legends of the accompanying illustrations. Much of the material is from patients over 40 years of age, but after assorting the specimens approximately 300 were available between 20 and 40 years. In studying the corpus luteum and the menstrual history together, we were able fairly accurately to approximate the day of cycle. We shall refer to this point later.

Schroeder in 1928 described the human ovarian cycle. He divides the ovary into various parts, into the germinal epithelium, the tunica albuginea, the cortex, and the medulla. With this description of the adult ovary most authorities agree. He illustrated a very interesting large section of a two-year-old whole ovary which we have copied to compare to one of similar age in our series. Quoting from Evans and Swezy, Schroeder felt that a great impulse is given to many follicles about the time that one or two are maturing. The small or medium follicles are more numerous when the large follicles are present and later when the corpus is formed. With this, our findings do not coincide. He also found that some, especially larger ones, become atretic, the greatest number of atretic follicles being found at the time of the formation of the corpus. These findings he considered rhythmical. Swezy and Evans feel that in some of their

cases the follicular cycle coincided with the menstrual cycle; that is, the number of ova present during the first few days was very small, and in others during the middle of the cycle the number was slightly larger and the maximum was reached during the last few days of the cycle. In the greater number of cases, however, they felt that there was no recognizable relationship between the condition of the ovary and the period of the menstrual cycle.

To review this point we selected specimens from individuals between 20 and 40 years of age. In the first place, during these decades the number of ova and the ovarian function are still adequate, but, because of the lesser number of ova than in the previous decades, we felt that differentiation as to what is actually going on could be better determined. Fifty selected cases were studied. The presence of small follicles, the condition of the tunica and germinal epithelium, the activity of developing follicles, and the character of the corpus luteum were studied in regard to variations in different parts of the menstrual cycle. A very detailed chart concerning these observations was prepared, but owing to the fact that it was quite cumbersome for publication, we decided to submit the results of this rather detailed study in the form of a summary.

In general, there was a very striking tendency for follicular activity to correspond to the menstrual cycle, more so in our series than Evans and Swezy indicated. The activity of the germinal epithelium and the tunica albuginea was definitely more pronounced in the early part of the cycle. The number of small follicles was more conspicuous in the earlier part of the cycle up to the time of usual ovulation. The developing follicles were most conspicuous just before the time of usual ovulation and continued more prominently till about the twenty-second day of the cycle. The histological characteristic of the corpus luteum fitted in very well with its time in the menstrual cycle. The number of small follicles did not go hand in hand with most mature follicle development as Schroeder contended.

The cortex was most interesting to us. It is described usually as connective tissue. For a long time one of us has contended that the cortex is not actually a connective tissue because it does not show the staining properties with van Gieson stain for such tissue, nor with Masson stain. In the van Gieson stain the cortex stains chiefly a yellow color as does ordinary smooth muscle tissue. A deeper red connective tissue stain is shown in the superficial portion of the ovary, namely, in the tunica. In many instances, the cortex and the tunica appear as one active cellular structure. In others, the tunica appears as a less cellular structure and frequently the tunica albuginea and the cortex are two clearly distinct zones. Almost invariably, with primordial or developing ova in the cortex, the staining reaction of the surrounding particle cells is much deeper and they appear definitely larger with this association than at other times. Intensity in nuclear staining is quite variable and we feel that the deep staining is most striking when functional activity is greatest. We regard the cortex not as smooth muscle nor as fibrous tissue, but as a hybrid tissue having some definite function as yet unknown.

Again, the details of our findings will be shown in our illustrations and are fully described in the legends. In reviewing our findings, we wish to state the following: In the first place, the germinal epithelium throughout the functional period of the ovary shows marked activity in growth, sending groups of cells which subsequently break off into the underlying tissue and finally reach the deeper cortex. New ova can actually be seen in association with this new development. The cells arrange themselves in perpendicular groups in the tunica immediately beneath the germinal epithelium, and subsequently invade. In the overlying tissue this activity does not involve the entire surface of the ovary, but rather occurs in spots. Whether these wandering cells, as we have termed them, develop into ova at once, or disintegrate immediately or subse-

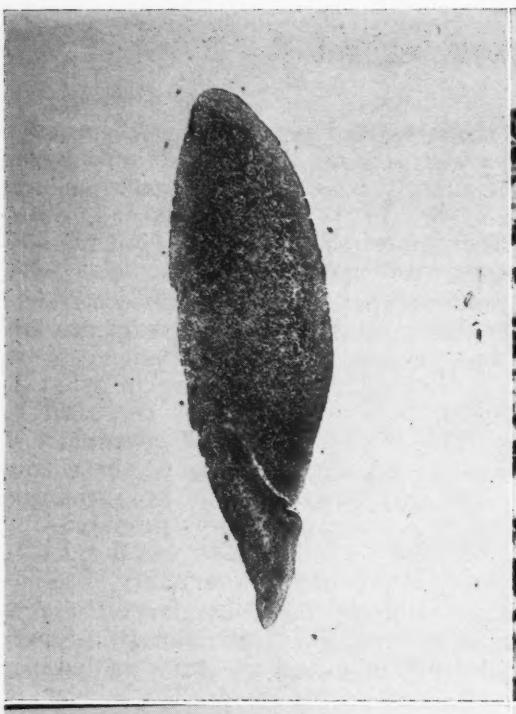

Fig. 1.

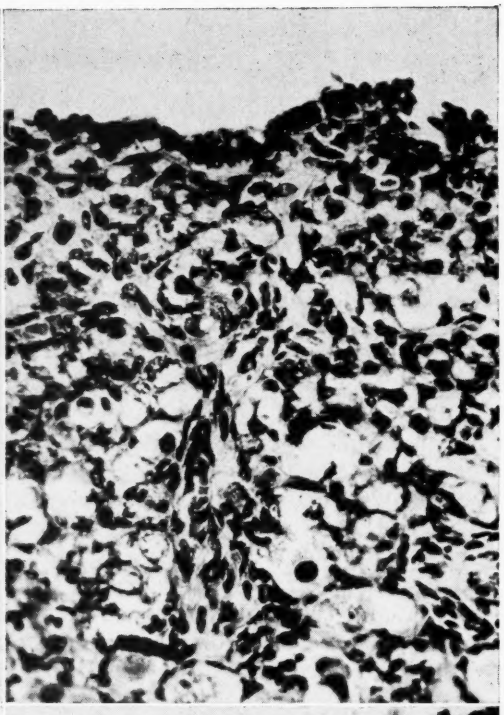

Fig. 2

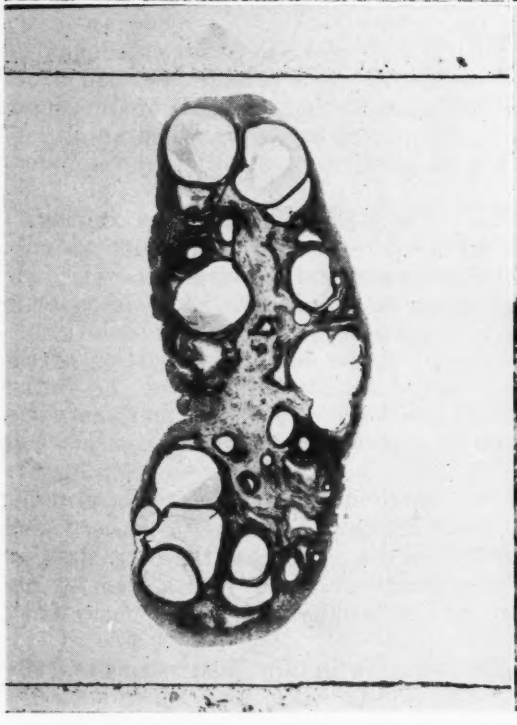

Fig. 3.

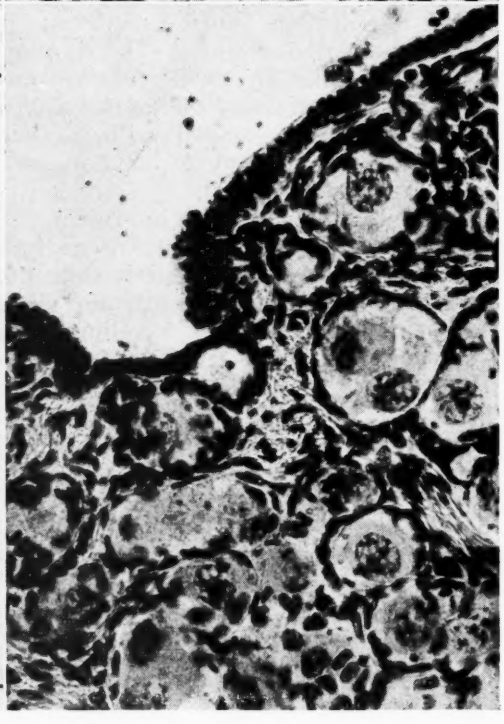

Fig. 4.

Fig. 1.—Ovary, six months' gestation fetus, section of whole ovary, active germinal epithelium can be seen in different areas. Main substance made up chiefly of primordial follicles (Simkins) with a small medulla being invaded by them. Cortex practically one mass of follicles.

Fig. 2.—Ovary, six months' fetus, low power showing active germinal epithelium on surface with underlying substance practically made up of primordial follicles, and some primary follicles.

Fig. 3.—Ovary, two years old, whole section, surface lined with thickened germinal epithelium, many small follicles in tunica and cortex, several large cysts undergoing cystic atresia. Cortex showing well; medulla comparatively small.

Fig. 4.—Ovary, two years old, high power, showing markedly active germinal epithelium with underlying tunica and cortex crowded with many primordial and primary follicles, structure of ova well seen. Note primary follicle just to right showing two ova encased in one follicle.

Fig. 5.

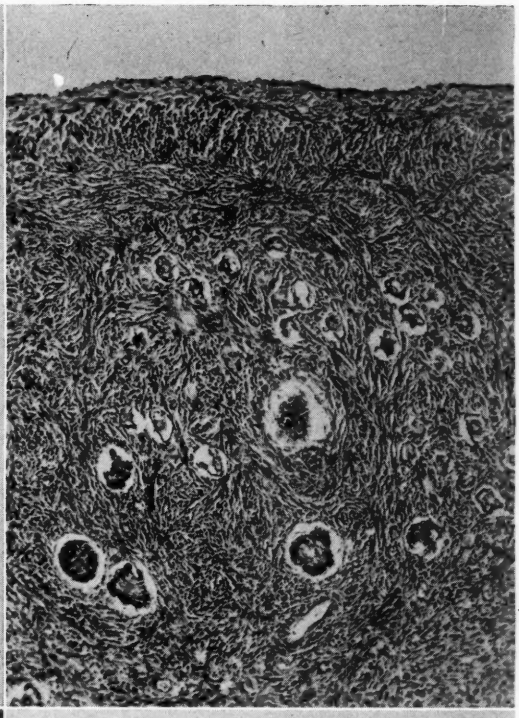

Fig. 6.

Fig. 7.

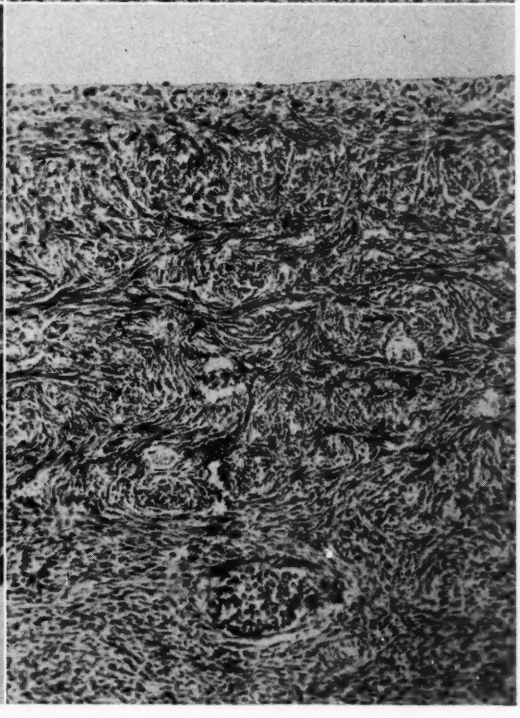

Fig. 8.

Fig. 5.—Ovary 12 years old, gross section whole ovary. Cortex and tunica well shown, medulla coming in from right center. Several maturing follicles dispersed evenly throughout the cortical portion of the section. Note the lower maturing follicle invading medulla.

Fig. 6.—Ovary, 12 years old, low power. Germinal epithelium flat, tunica active, numerous primary follicles in superficial cortex, with cell nests and more advanced follicles showing in deeper cortex.

Fig. 7.—Ovary, 19 years old, gross picture, showing larger portion of ovary. Medulla coming in right central portion. Numerous scattered cystic follicles, some invaded into medulla. No fresh corpus luteum seen, but one present from previous ovulation.

Fig. 8.—Ovary, 19 years old, low power. Germinal epithelium flat, tunica contains large light-staining cells, well differentiated from underlying cortex. Only a few primary follicles in the field; note large cell group in lower center.

Fig. 9.

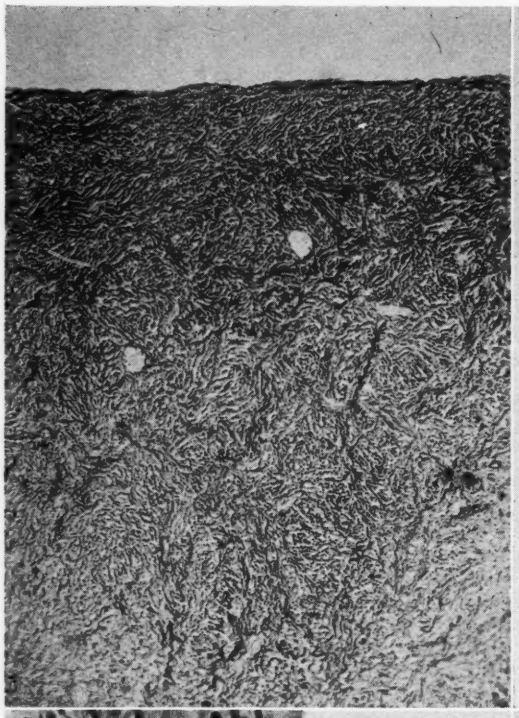

Fig. 10.

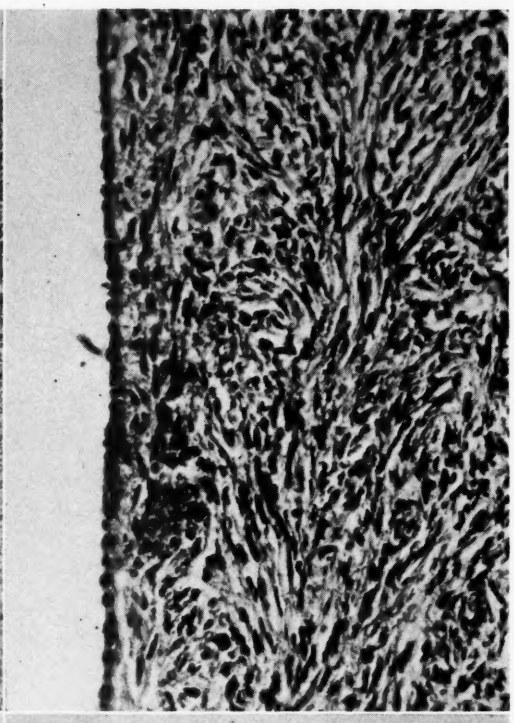

Fig. 11.

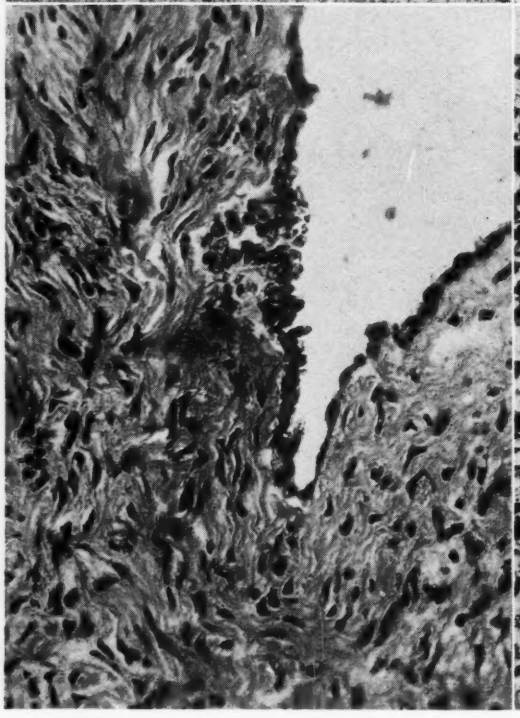

Fig. 12.

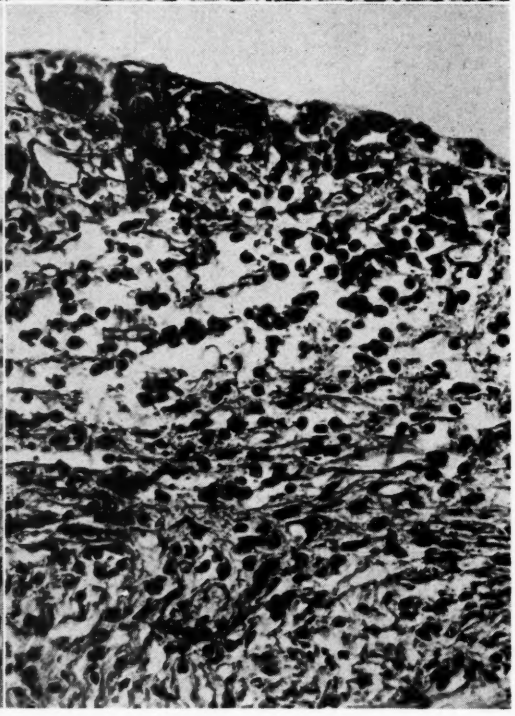

Fig. 9.—Ovary, 19 years old. Van Gieson stain, small amount of connective tissue in albuginea, black in picture. Note much lighter cortex, actually staining yellow like smooth tissue.

Fig. 10.—Ovary, age 24 years. Surface low cuboidal epithelium left, tunica and cortex as one not active. Fourth day of cycle.

Fig. 11.—Ovary, age 45 years. Active germinal epithelium with invasion of tunica albuginea.

Fig. 12.—Ovary, age 22 years. Surface showing marked germinal epithelial proliferation with invasion, showing ova in largest penetrating cell mass.

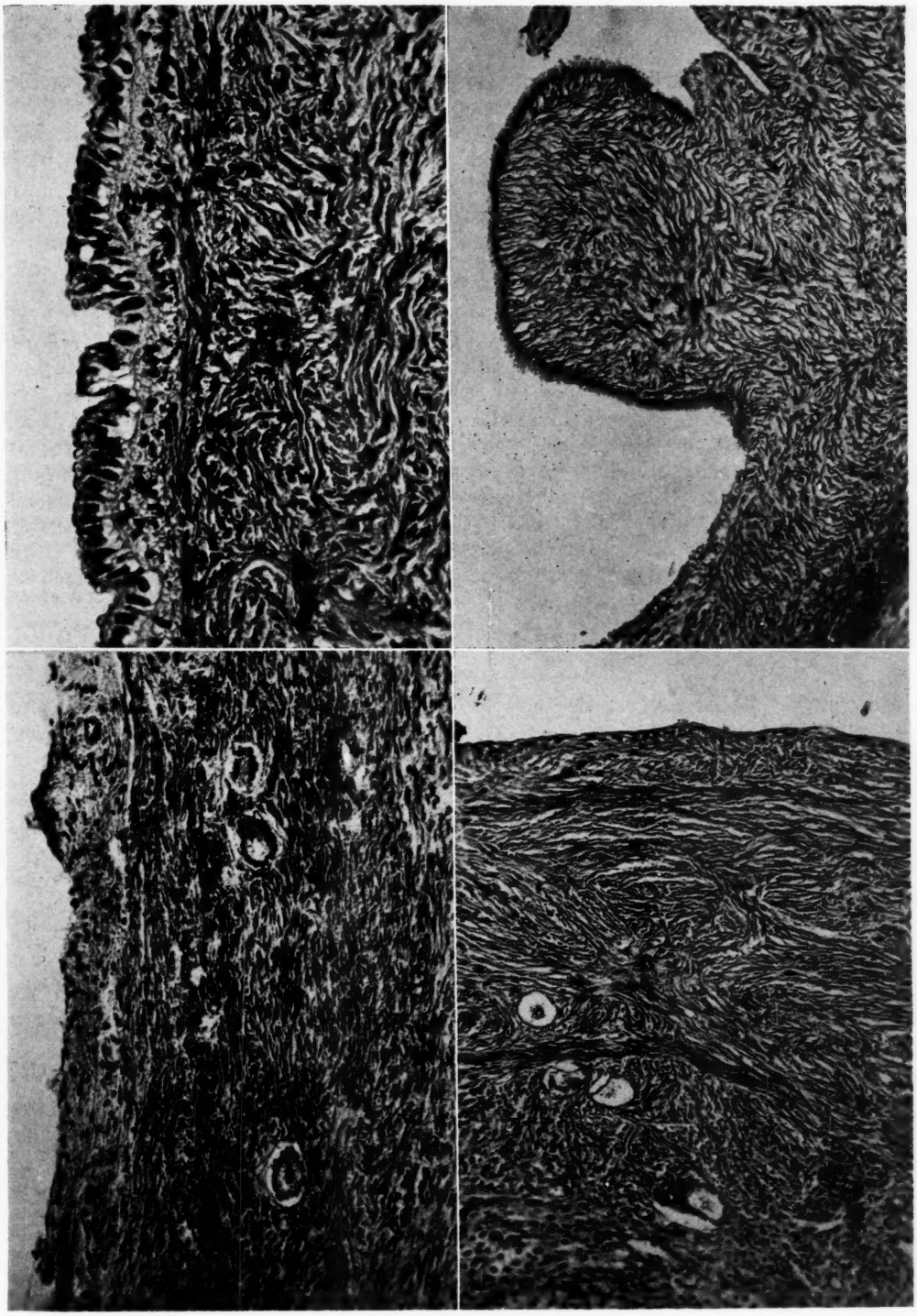

Fig. 13.

Fig. 14.

Fig. 15.

Fig. 16.

Fig. 13.—Ovary, age 28 years. Surface to left, marked activity of germinal epithelium with striking invasion of numerous cells in tunica albuginea. Differentiated ovum under epithelium in upper left of picture.

Fig. 14.—Ovary, age 45 years. Germinal epithelium fairly high, cortex and tunica as one, made up of diffusely scattered light-staining spindle cells.

Fig. 15.—Ovary, age 28 years. Tunica and cortex. Surface to left. Note ovum in middle of tunica. More advanced primary follicles in upper cortex. Tunica not very active. Germinal epithelium lost by artefact.

Fig. 16.—Ovary, age 21 years. Shows distinct active tunica, follicles penetrating deep in the cortex. Note deep cortical reaction about them, and also developing ovum at bottom of picture.

quently, we do not definitely now. It is frequently very difficult to determine whether cells are actually cells of the cortex per se or penetrating cells. We rather feel that the wandering cells become intermingled with the cortical cells and differentiation of these cells in many instances is not possible, chiefly due to similar intensity in staining reaction.

We believe that the idea of Simkins is quite possible. However, with the activity of the germinal epithelium and the tunica, along with the appearance of primary and primordial follicles in the tunica, which make their way into the deeper cortex, we are inclined to believe that the observations of Evans and Swezy meet the facts more directly. Conceding that new ova are formed which develop and become functioning after adolescence, it immediately places importance on the treatment of certain conditions with the use of the anterior pituitary preparations stimulating the ovarian follicular apparatus. This would involve cases of amenorrhea, sterility, and the anovulatory cycle. It would seem that, with the idea that the functional apparatus begins to show activity shortly after menstruation, reaching its maximum approximately a few days after ovulation, proper therapy and dosage would be most important, especially as regards intensity and timing. Accordingly, it might be reasonable to start the therapy in the middle of the actual menstruation, or before, continue rather vigorously for four or five days, and then gradually diminish it until about the tenth or eleventh day of the cycle.

Conclusions

We feel from this review of our own material that the work of Evans and Swezy and Simkins concerning the development of the new ova after birth and in active adult life can be definitely accepted. So far as the origin of these cells is concerned, we conclude that they have their origin in the main from the germinal epithelium. The cortical source of these cells as suggested by Simkins cannot be discarded; this origin is more difficult to demonstrate. We believe both sources are quite possible, but this can be determined only by further special study of the cortex with this single point in mind.

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Discussion

DR. JEAN PAUL PRATT, Detroit, Mich.—The story of the development of the definitive ovum is long and complicated. Since it is not possible to follow the process continuously in a single individual, the concept of ovogenesis is derived by piecing together fragments obtained from the study of many individuals and numerous species. Some phases are generally accepted while others are the subject of opposite opinions. Some anatomists and embryologists maintain that the earliest sexual cells are seen in the hindgut of early embryos from whence they migrate to the site of the future gonad. Here they are assumed to form or influence the formation of the future ovum. Others deny the existence of such migrating sexual cells. There is agreement, however, that the germinal

epithelium of the gonad is derived from the celomic epithelium. Furthermore, thousands of primordial follicles are formed during early intrauterine life. It has been accepted that most of the follicles degenerate at one time or another. Whether these follicles persist throughout the reproductive life and some of them mature with each menstrual cycle remains debatable. Also the time at which the formation of primordial follicles ceases has been variously placed at early embryonic life, throughout fetal life, the first year of postnatal life, up to puberty, and throughout the mature reproductive period.

Among early observers who published fragmentary evidence that ovogenesis occurred in adults may be mentioned: Pfluger (1863), Schron (1863), Koster (1868), Slavinski (1873), Wagener (1879), Van Benedin (1880), Amann (1899), Palladino (1898), Kingery (1917), Robinson (1918), and Arai (1920).

Edgar Allen (1922), having studied intensively the estrous cycle of mice, thought that they would be an excellent animal to observe for ovogenesis. He reasoned that the mouse has a greater fecundity than most other mammals; it has one of the shortest estrous cycles; the ovary is very small, facilitating complete examination, and the surface epithelium is well protected by a complete periovarian capsule. From Allen's observation on the ovaries of sexually mature mice he divided ovogenesis into three stages: (1) mitoses in the germinal epithelium, (2) small ova just under the germinal epithelium about which a few follicle cells are grouped, and (3) ova similar to the above but two cells below the surface of the ovary. The maximum incidence of the first stage was at estrus. Transition through the three stages required four to six days, i.e., one estrous cycle. Thus Allen established for the first time cyclic ovogenesis in sexually mature mammals.

In 1928, while Allen and I were examining human ovaries removed at the midmenstrual period, a search was made for mature follicles, early corpora lutea, and evidence of ovulation. The first stage of ovogenesis was observed occasionally. Evidence of the second and third stage was inconclusive. Compared with mice we found the study of human ovogenesis far more difficult because: (1) The number of ova developing in each cycle is less; (2) the human ovary is not so well protected, making it difficult to preserve the germinal epithelium intact; (3) the menstrual cycle is relatively long; and (4) the size of the ovary makes a complete examination laborious. The evidence we obtained was suggestive but we felt it was too meager to justify publication. The work of Evans and Swezy, to which Dr. Schwarz referred, is intriguing but not convincing so far as human ovogenesis is concerned.

A clear distinction should be made between ovogenesis on the one hand and follicular development through ovulation and corpus luteum formation on the other hand. The process of ovogenesis is inherent within the ovary and is not under control of the pituitary gland. The sequence of events seen in the formation of primordial follicles is probably brought about through the interaction of a self-contained system of organizers within the growing follicle. The nature of such organizers is not known but the existence of organizers is generally accepted. Only when follicles are developed to the antrum stage are they susceptible to the influence of the pituitary gland.

That the ovaries of young animals are refractory to gonadotropin is appreciated when selecting animals for pregnancy tests. Rabbits under 12 weeks or 1,200 Gm. are refractory. Rats and mice under 16 days are refractory. Even some older and larger animals are refractory.

Follicles above the antrum stage vary in their susceptibility to pituitary hormones. With a small dose only the large follicles respond. As the dose is increased the younger follicles respond but primordial follicles never respond. Hypophysectomy of adult animals is followed by atresia of all the follicles with antra and larger but the primordial follicles are not affected. The mammalian ovum may attain its full size in hypophysectomized animals. The absence of pituitary control over ovogenesis and early development of follicles is probably true of all vertebrates. We cannot hope to influence or control ovogenesis until we learn something of the nature of organizers.

The fragment of evidence that ovogenesis occurs in the germinal epithelium of the adult is a distinct contribution. I hope that Dr. Schwarz will continue his laborious efforts.

DR. EMIL NOVAK, Baltimore, Md.—Dr. Schwarz's paper represents a valuable contribution in a field in which there was clear need for further investigation. Since the publication of the paper of Evans and Swezy many years ago, based as it was on studies on lower animals, there has been almost no systematic effort to investigate human ovaries from the same viewpoint. Following the report of Evans and Swezy, I looked unsuccessfully for evidence of postnatal ovogenesis in the routine examination of ovaries, but a more intensive investigation is necessary before any conclusion can be drawn, and the present paper represents a study of this sort.

The question of ovogenesis is bound up with two other questions, concerning both of which there is still difference of opinion. First, there is the question of whether the germ cells have their origin in the so-called germinal epithelium of the ovary, or whether they migrate to the ovary by way of a *Keimbahn* from a much earlier situs in the primitive hindgut. The latter origin has been definitely established in certain lower animals, and the evidence for the existence of a *Keimbahn* in the human being is becoming increasingly strong.

The second question is as to whether the early sex cords and the Pflüger tubules are produced by invagination from the germinal epithelium, or whether, as now is accepted by most embryologists, these structures are formed by differentiation in situ from the ovarian mesenchyme, which would explain the origin and the histological and clinical characters of certain special ovarian tumors, as I have elsewhere discussed.

Whatever the original source of the germ cell may be, it may still be true that some degree of accessory ovogenesis may arise from the germinal epithelium. Gruenwald, incidentally, has described certain accessory sex cords arising from the surface epithelium, although he arrives at no definite conclusion as to their significance. Dr. Schwarz's slides are highly suggestive, but his own conclusions are still conservatively tentative, so that I hope he will continue his studies in this hitherto almost neglected field.

DR. ROBERT CREADICK, Durham, North Carolina.—Twelve years ago when I was a pupil of Dr. Edgar Allen we initiated a study as a principal *arbeit* on my part by experiments on rats, mice, and monkeys. Upon occasion I feel that the anthropoid apes are not so far below us. I think the application here might be well put. The alkaloid colchicine was employed, which has the capacity of arresting dividing cells in metaphase. It was almost as though we were using radioactive tracers on the immature female animals to find out which parts of the genital tissue responded. The stimuli used were Prephysin (APL) and pregnant mares' serum. The response was magnificent. I do, however, feel that the continuance of our studies was rather against Swezy and Evans' report.

Cyclic ovogenesis does occur and our control animals which were sacrificed showed practically no evidence of ovogenesis. Active mitosis did occur in the germinal epithelium of ovaries of the mature mouse at estrus. It seems to be a fundamental process.

DR. SCHWARZ (Closing).—Referring to the question that Dr. Pratt raised about mitosis in the ovary after birth, I personally did not see any evidence of mitosis nor did Swezy and Evans, but both Evans and Simkins studied minutely the nucleus of the ovum before birth and they found mitosis then.

After birth, the only other phases of further maturation are noted in the ovum at ovulation with the formation of the polar bodies and their extrusion so well shown by Pratt and his co-workers. Swezy and Evans and Simkins have pointed out that ova may divide, but by amitosis, and I have seen evidences of that in some of my sections where there develops a sort of dumbbell nucleus just as it is about to split in two.

PERSPECTIVES IN PREMATURITY*

Physiological Approaches to an Obstetric Problem

S. R. M. Reynolds, Ph.D., Baltimore, Md.

(From the Department of Embryology, Carnegie Institution of Washington)

FOR the conventional obstetrician, prematurity poses three chief problems. First is recognition and treatment of premature labor; second is the immediate and ultimate care of the premature infant; and third is the real, compelling truth of the statistical aspect of the subject. Prematurity alone ranked as the ninth single cause of human death in the United States in 1945 and there is no reason to suppose that this situation is materially different today.

For the physiologist, there are likewise three major problems centering about the larger one of prematurity. These are: (1) the characteristics and control of uterine growth during pregnancy; (2) the provision for the nutrition of the fetus; and (3) the complex question of muscular power for emptying the uterus of its contents at term, and not before. Taken together, these factors comprise the principal elements of what we may call the physiologic process of uterine accommodation of the products of conception. At all times, these elements must be so interrelated and integrated that they provide a uterine environment suited to the needs of the embryo and fetus if it is to develop normally. What, then, are the elements of uterine accommodation?

Elements of Uterine Accommodation

When a fertilized ovum enters the uterus and becomes attached to the endometrium, it finds this tissue prepared structurally and functionally for nidation. The main features of this are generally known to medical men. Then a series of complex changes begins to unfold. These are so interrelated that, taken together, they provide room for the unborn until the end of gestation. The main features of these changes are not generally known to medical men, and most obstetricians are inadequately informed regarding them.

Uterine growth is the most obvious of these changes. The human uterus increases in size from an organ weighing about an ounce and one-half to one weighing over one and one-half pounds. While the uterus makes room for the unborn by extensive growth of tissues, it develops at the same time great contractile power. Normally, this remains dormant throughout most of pregnancy for a time which is fixed for each species. In this we witness the instructive spectacle of a growing force intended to overcome at a definitely future time a definite resistance, against which it never measures its strength until the actual moment of conflict has arrived.

Throughout this time, a continuous and adequate amount of maternal blood is supplied to the placenta in order to sustain the life of the unborn

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child, and to provide abundantly for its growth. We may consider with profit, therefore, the salient characteristics of uterine growth during pregnancy, since this is the back-drop against which the drama of fetal development is played.

Uterine Growth and Uterine Accommodation

According to prevalent notions, the uterus accommodates the products of conception by progressive uterine growth from early pregnancy to its end. The view is generally—though erroneously—held that the uterus is able to grow almost indefinitely. Actually, we now know that there is a limit to the amount of growth taking place during pregnancy; that this is related to the degree and shape of the distending conceptus, and that the contractile power of the uterus at term is sufficient and little more to dilate the cervix during labor. The evidence for this is of the following sort.

The curve of uterine growth during pregnancy in the rabbit is shown in Fig. 1. The principal period of uterine enlargement occurs between the time of implantation and the twenty-fourth day of gestation (Reynolds, 1946). From this time until term there is little further uterine enlargement, yet this coincides with the time of most rapid fetal growth. This last phase, therefore, is a period of uterine stretching. Is this a generally applicable phenomenon?

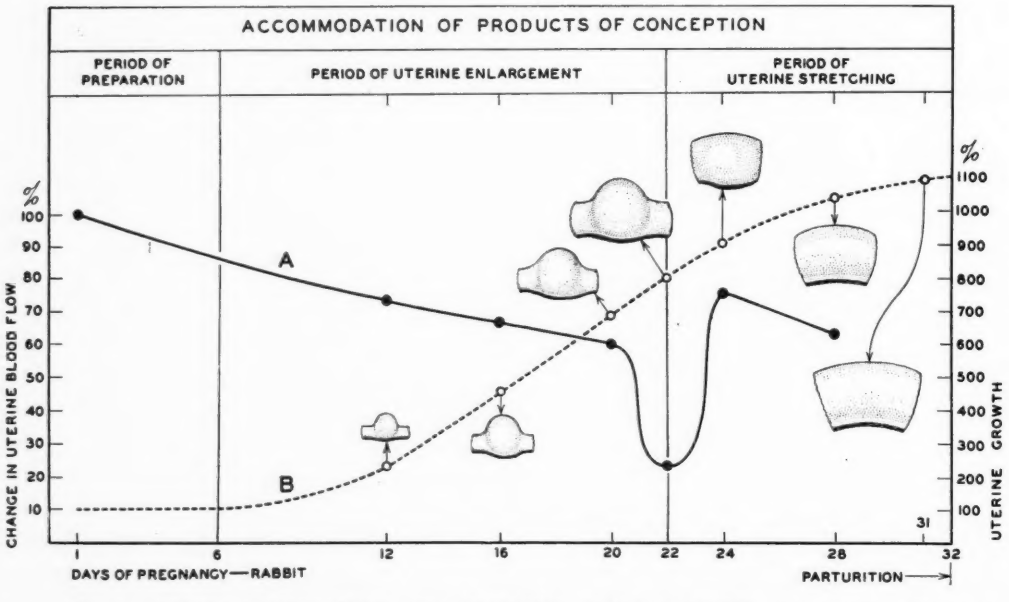

Fig. 1.—Uterine accommodation and circulation of blood through the uterus. Curve A, local blood flow through the lateral uterine vein in the uterine wall; B, increase in weight of the uterus during pregnancy, showing the relative size and shape of the conceptus at different times. See text for description. From AM. J. OBST. & GYNEC. 53: 901, 1947.

The limited evidence that we possess from various animal species suggests that it is. For example, in the rat and cow, data show that some limitation of uterine growth occurs toward the end of gestation, when the fetus is increasing most rapidly in size (Reynolds, 1940). Similarly, consideration of a few data from the human being and the rhesus monkey shows that the

pattern of uterine enlargement is rather like that of the rabbit (cf. Fig. 2; Reynolds, 1947). In short, we may say that in normal pregnancy, there comes a time when the size of the fetus becomes too large for its environment. That is the first aspect of uterine accommodation which is to be emphasized.

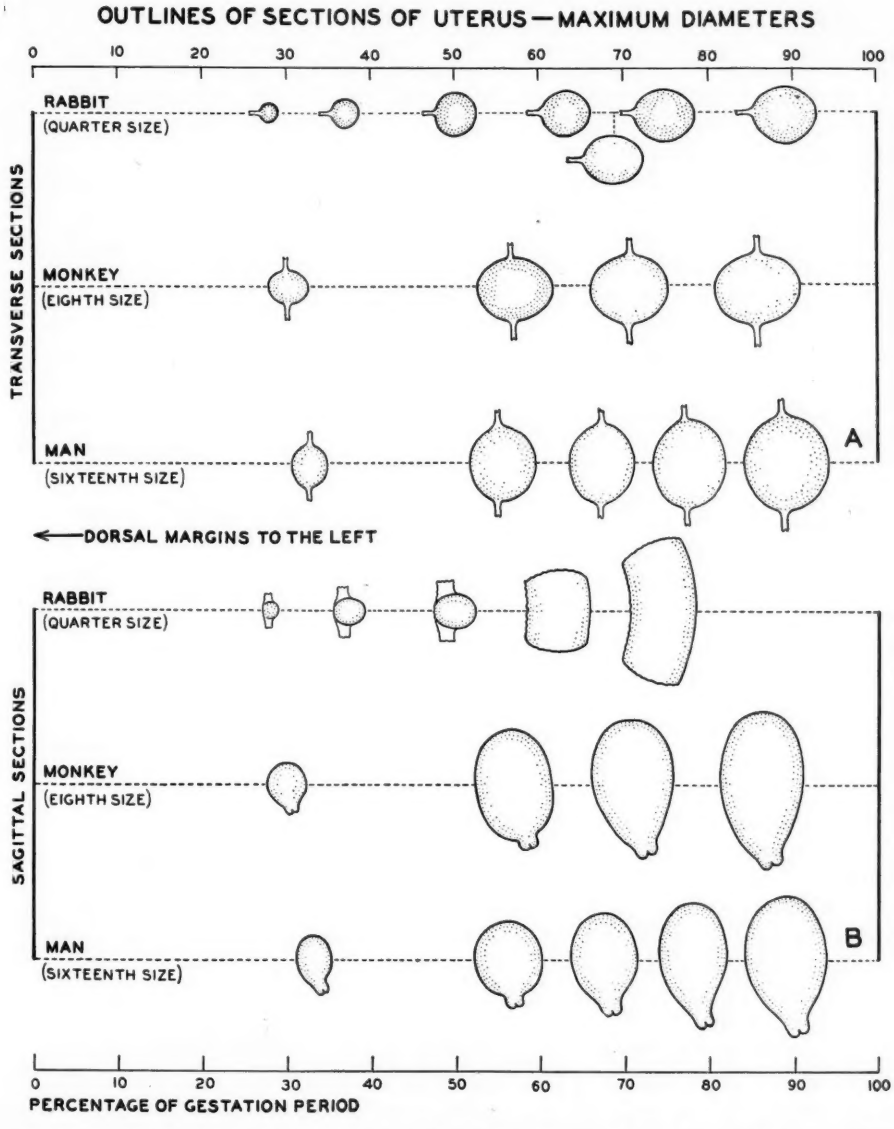

Fig. 2.—Diagrams showing the three-dimensional growth of the rabbit, monkey, and human uterus followed in the last part of pregnancy by a period of elongation. Top, cross-section, bottom, sagittal sections through the middle part of a conceptus. From AM. J. OBST. & GYNEC. 53: 901, 1947.

There is a second aspect of uterine growth that must be mentioned. In Figs. 1 and 2, it is shown that during the period of uterine enlargement the conceptus is spheroidal. During the period of uterine stretching, it is elongated and cylindrical in shape. Clearly, the *shape* of the uterus is a factor which plays a role in uterine accommodation along with uterine growth.

Shape of the Conceptus and Uterine Accommodation

The shape of the uterus about a newly implanted conceptus is that of a small spheroid increasing rapidly in three dimensions. In the latter part of pregnancy in the rabbit, it is one of a cylinder, the size of which increases for the most part in but one dimension, namely, length (Reynolds, 1946).

This point is worth emphasizing for two reasons. First, the uterus behaves physically just like a hollow elastic membrane. Second, since the membrane is subjected to varying patterns of stress according to the predominant hormone influence at any time and the shape and size of the uterine contents, the resistance offered to the flow of maternal blood through it varies from time to time (Reynolds, 1947).

With respect to the first of these facts, the membranelike qualities of the uterus, our attention centers on the nature of the process of *conversion* from spheroid to cylinder. It has been established positively in the rabbit that this takes place within the space of a few hours (Reynolds, 1946). This means that the uterus is subjected to increasing tension until a critical condition develops. Then suddenly by changing shape the conceptus reduces the resistance to its growth imposed upon it by the spheroidal membrane which surrounds it on all sides with increasing tension, and it is then restricted in the cylindrical form by the confining action of the tissues of the uterus along its length. This situation is analogous to that of a long, sausage-shaped balloon blown with great force to a maximum spheroidal size near the mouth and then, when the internal pressure is sufficient, the balloon opens up with ease along its entire length. The pressure required to distend the elongating balloon immediately after conversion is then but a fraction of what is required to blow up the balloon when it was a sphere just prior to conversion. Physically, these relationships are approximately and in part as follows (Reynolds, 1946):

$$T_s = \frac{r^2 \cdot p}{2}$$

and

$$T_l = \frac{r \cdot p}{2}$$

where T_s is the tension to be overcome by the pressure, p, in the sphere, and T_l is the tension to be overcome by the pressure, p, in the cylinder as it lengthens. The first is a geometric function of the radius, the second is a linear function of the radius. This means that, in the first instance, tension is proportional to the square of the radius, and in the second, it is directly proportional to the radius.

We see, therefore, that the growth of the conceptus during the period of greatest uterine growth is against increasing tension all around, whereas, during the period of rapid fetal growth and uterine stretching, the tension is reduced to a minimum. The mind must be peculiarly constructed which fails to see in this a marvelous provision of Nature to permit maximum fetal growth against the least possible obstacle in the latter part of gestation, and it is an excellent example of the Principle of Least Work in nature, in which work is accomplished at the lowest level of expenditure of energy possible.

The correctness of this interpretation has been proved in several ways but only one will be described here. In one set of experiments, the dye, Prussian blue, was injected into the uterine blood vessels under fixed conditions. This dye is freely diffusible, so if it enters the blood capillary vessels it should stain the surrounding tissues. It has been found (Reynolds, 1948) that until the twentieth day of pregnancy, the entire uterus is evenly injected

with the dye. On the twentieth and twenty-second days, the areas over the most distended regions of the uterus are not stained. Immediately after conversion there is again even penetration of the dye into all tissues, however distended they may be. Thus the conceptus changing shape by its own continued growth normally creates its own favorable environment for further growth, and this is by virtue of its change in shape. This *conversion* of the uterus from one form to another at a given point in pregnancy marks a physiological change of some moment in uterine accommodation.

Conversion and Uterine Accommodation

Conversion takes place in all types of uteri. Fig. 2 shows that three-dimensional growth in the monkey and human being takes place about sixty-five per cent of the way through pregnancy. Recent work in collaboration with Dr. E. M. Ramsey by means of soft tissue x-rays and direct observation of the uterus in monkeys shows that conversion occurs somewhat, but not much, earlier than is indicated in Fig. 2.

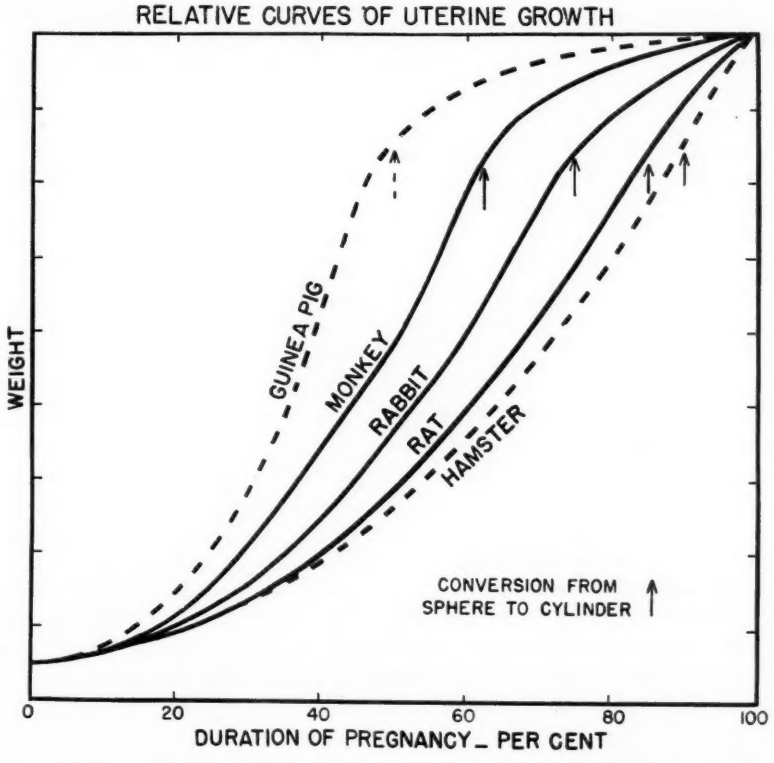

Fig. 3.—Schematic diagram of the relative curves of uterine growth in a group of widely divergent animal species. The time of conversion in each is indicated by the arrow. Dotted lines signify curves for which data are not yet adequately available. Observe that the earlier the time of conversion, the longer is the period of uterine stretching (i.e., relatively little uterine growth during the period of very rapid fetal growth).

Looked at another way, I have taken the liberty of plotting schematically in Fig. 3 the relative curves of uterine growth and the time of conversion in each from a number of widely divergent species. Additional observations will have to be made to increase and extend the precision of some of these curves. With these reservations in mind, the curves shown in Fig. 3 are of-

fered tentatively to indicate the definitely established time of conversion in each species, and what appears to be the best evidence concerning the form of the uterine growth curve.

Here, the reader will see that the forms of the uterine growth curves are not the same for all species. The hamster and rat stand at one extreme; the monkey and the guinea pig at the other. The significant thing is that the earlier the time of conversion in gestation, the longer is the period of relatively little uterine growth. The significance of this will be clear from what has been said above: *the duration of the period of uterine stretching depends upon, and is proportional to the period of rapid growth of the fetus.* It marks, therefore, the beginning of accelerated fetal development, and *its occurrence should serve as an index of fetal maturity at birth.* More shall be said of this later, however.

Fetal Maturity at Birth and Uterine Accommodation

The significance of the conclusion just stated is clear. If it is true that conversion may serve as an index of fetal maturity at birth, then we may postulate a relationship—in the terms of physiology of another day, a law—of fetal maturity at birth. It would rest upon the fact that fetal maturity at birth is proportional to the total duration of pregnancy which the fetus spends in an elongating uterus. What is the evidence that such a relationship may exist?

The evidence at hand is fragmentary and as yet incomplete. Much more must be learned before we can state it to be a fact. The data at hand are intriguingly suggestive, nevertheless. In the first place, the durations of pregnancy in the hamster, rat, rabbit, and guinea pig are, respectively, as follows: 15.5 days; 21 days; 32 days; 65 days. The proportions of pregnancy spent in a cylindrical uterus are, in the same order, 1/9th-1/10th for the hamster; 1/7th for the rat; 1/4th for the rabbit; about 1/2 for the guinea pig.

If one considers the maturity of the newborn of these species, one is impressed with the degrees of maturity which range from no sex differentiation of the external genitals in the hamster, to maturity in the guinea pig which includes temperature regulation, righting and postural reflexes, a coat of fur, and the ability to take food other than its mother's milk. At the present time, L. T. Bradin, a graduate student at Johns Hopkins University now working in the Carnegie Laboratory, is procuring systematic data on this subject by studying degrees of ossification before, at, and after birth in relation to the proportion of pregnancy the fetus has spent in the cylindrically shaped uterus. Enough is known to say now that a hamster about the fifth day after birth is comparable to a newborn rabbit in terms of ossification of the bones in the feet and equal to a 2-day-old rat. In other words, by adding some five postnatal days in the hamster to the one and one-half prenatal days in the cylinder, we find that the hamster on the fifth day after birth has lived about 31 per cent of its post-conceptional life in what may be called a "post-spheroidal" existence. The rabbit at a comparable stage of development (birth) has lived about 28 per cent of its post-conceptional life in a "post-spheroidal" existence and the rat, some 26 per cent. These relations are summarized in Table I.

Other data suggest the validity of a relationship between fetal maturity and the time of conversion also. The sensitivity of the newborn to anoxia is being used by Bradin to test it. It is a well-known fact that the less mature the newborn, the greater is its tolerance of anoxia, and vice versa.

TABLE I. COMPARATIVE MATURITY OF THE NEWBORN*

CRITERION: EQUAL OSSIFICATION OF METATARSAL BONES				
COLUMN	FACTOR	HAMSTER	RAT	RABBIT
A	Duration of pregnancy, days	15.5	21	32
B	Days post partum	5	2	0
C	Conception age (A + B)	20.5	23	32
D	Conversion of conceptus, day	14	17	22-24
E	Days in cylindrical uterus	1.5	4	9
F	B + E	6.5	6	9
G	Per cent of gestation age post sphere $\frac{B + E}{C} \times 100$	31.1%	26.0%	28.1%

*Bradin: Work in progress.

The data of Table II show the duration of respiratory effort in an atmosphere of nitrogen for the hamster, rat, cat, dog, rabbit, and guinea pig. Data on the time of conversion in these forms are available only in the case of the hamster, rat, rabbit, and guinea pig. It is clear that the immature hamster breathes much longer than the more mature rabbit. Some hamsters, in fact, have breathed for more than an hour in pure nitrogen. Much more work will have to be done, however, to establish the degree of correlation between these physiologic attributes of maturity and the time of conversion in the course of uterine accommodation.

TABLE II. RELATION OF UTERINE ENVIRONMENT TO ANOXIA TOLERANCE OF NEWBORN

SPECIES	DURATION OF PREGNANCY DAYS	PROPORTION OF PREGNANCY IN CYLINDRICAL UTERUS	SURVIVAL IN NITROGEN (MINUTES)	
			BRADIN*	HIMWICH ET AL.
Hamster	15.5	1/9-1/10	35+	
Rat				
Albino	21	1/7	15-20	50
Cotton†	27	—	11	
Cat	52	—		25
Dog	63	—		23
Rabbit	32	1/4	10	
Guinea pig†	63	ca. 1/2		7

*Work in progress.
†Relatively mature at birth.

Another aspect of maturity which promises to lend itself to fruitful investigation is that of the development of reflexes. For example, the hamster and rat are devoid of postural (but not righting) reflexes at birth, whereas in the monkey and guinea pig these are well developed, in the latter rather more than in the former. This, too, compares qualitatively with the proportion of life spent in postspheroidal development.

There are two further points of comparative development to be mentioned which reveal that a maternal factor, not defined, controls the maturity and size of the fetus at birth. Many years ago the Dutch geneticist, Hagedorn, then of the University of California and now of Soesterberg, Netherlands, cross-bred wild hares with domestic rabbits. The offspring of the former are born with eyes open, a full coat of fur, possessing jumping and postural reflexes and the ability to eat food other than mother's milk. The duration of gestation is about fifty-six days. The appearance of the helpless

newborn rabbit is too well known to require comment here. The duration of pregnancy is thirty-two days. When a male hare is bred to a female domestic rabbit doe a most interesting physiologic phenomenon results. The young are born in thirty-two days in the same helpless immature state that newborn rabbit pups are.

A second evidence of maternal control of fetal size at birth is that reported by Walton and Hammond (1938) pertaining to the cross-breeding of large Shire horses and small Shetland ponies. Although the duration of pregnancy is not affected, it is found that the breeding of a Shire stallion to a Shetland mare results in offspring always of the same size as newborn Shetland ponies. In these two instances we witness evidence of some physiologic maternal mechanism which controls and determines the size, and hence the maturity, of the offspring at birth. I submit that there is no other known mechanism than that of uterine accommodation as outlined above by which these facts may be explained.

Uterine Accommodation and Uterine Circulation of Maternal Blood

There are other aspects of uterine accommodation and prematurity which must be mentioned in a general discussion of fetal maturity.

The process of conversion brings about a favorable physical environment for fetal growth. How does this affect the circulation of maternal blood through the uterus?

Fig. 1 summarizes the results of experiments designed to test this point. By means of a standard physiologic technique, an estimate was made of the rate of blood flow through the tissues about the most distended parts of the uterus. One can see that progressive increase in the size of the conceptus is associated with an attendant decrease in blood flow until the time of conversion. Then there is a sudden, intense but transient decrease in the flow of blood through the uterine blood vessels. Following conversion with its attendant relief of tissue tension and opening up of smaller blood vessels, the rate of blood flow is restored to a level comparable to that seen earlier in pregnancy.

Why, one asks, is not the welfare of the fetus endangered at the time of this reduced uterine circulation? In some cases it is, for it is at this time that we begin to find resorbing fetuses in the latter part of pregnancy. Normally there are mechanisms which guard against this eventuality by virtue of a localized circulation to the placenta which is actually favored at the time the rest of the uterus experiences profound ischemia (Reynolds, 1948). The extent to which these facts apply to the *uterus simplex* of the primate is wholly unknown today.

Uterine Contractility and Uterine Accommodation

In addition to the factors of uterine growth and fetal nutrition, the proper employment of the contractile powers of the uterus must be achieved in order to permit development of the fetus to full maturity, on one hand, and effective delivery at the time of parturition, on the other. We are just now in position to study these aspects of myometrial activity. An instrument for studying the patterns of activity of the entire uterus is now available (Reynolds, Heard, Bruns, and Hellman, 1948) and will be used to study uterine contractility in normal pregnancy and in its complications.

The characteristics of uterine contractions which are effective in dilating the cervix during labor are now known, and some of the attributes of ab-

normal patterns of uterine activity, in false labor, premature labor, and so forth, have been described (Reynolds, Bruns, and Hellman, 1948).

But knowledge of these patterns raises new and different problems to be investigated. For example, what hormonal and physical factors control normal and abnormal patterns of uterine cavity? To what extent does the innervation control them? And finally, by what therapeutic means may premature and incoordinate activity of the uterus be controlled? Until answers are forthcoming to these and other questions, we may truly be said to be in the dark concerning the real role of uterine contractility as a contributing factor to prematurity.

A Clinical Sign for Fetal Maturity?

With what practical point may the obstetrician concern himself, after the physiologist has indicated the avenues into which review of the problem of fetal maturity leads him? The cardinal fact which seems ripe for exploitation pertains to the relationship between conversion and subsequent fetal maturity at birth. We have seen that three-dimensional uterine growth ceases in the human being between six and seven tenths of the way through the course of pregnancy. If the obstetrician could know to within a week when this occurs, he would then know that every week after conversion is an added guarantee of full maturity and so viability of the baby at birth. His whole concept of the relation of fetal maturity at birth to the duration of pregnancy would be altered in the direction of certain knowledge in a matter which now entails what may be termed in the diplomatic language of World War I, "watchful waiting."

What the obstetrician needs is some concrete, palpable physical sign of conversion. What shall it be? Obviously uterine size is not suitable, since a small uterus may convert at a relatively earlier time than a large one and so give birth to a mature infant in a pregnancy of short duration. Shape of the uterus is the important thing. This presents difficulties in its estimation, particularly where three-dimensional growth must be considered.

It may be that a useful criterion of this will be found in one of the physical signs which is known to present itself in rabbits and in monkeys and so, probably, in women, too. It is that just prior to conversion the uterus is firm and tense; immediately after conversion it is loose, flabby, and soft. This is the result of the sudden diminution of uterine tension because of the change from a shape in which tension is a geometric function of the radius of curvature to one in which it is a linear function. The change is transient, however, since fetal growth will again take up the slack during the period of uterine stretching. This transient softening of the uterus, therefore, could be a clinical sign of first importance, if it is possible to judge this subjectively. But there no doubt are physical limitations to palpating the body of the uterus where the principal softening occurs. If this should be an impossible physical sign to employ, what others remain?

Clearly, this must be a matter for the obstetrician to decide. Perhaps during the sixth and seventh month abdominal profiles with the subject in a favorable position may reveal a characteristic change which is related to the process of conversion. Or again, uterine souffle, which now has no known physiologic or renal clinical significance, in some way may be found to betoken an alteration in hemodynamic conditions in the uterus which is related to the period of uterine stretching during the last part of pregnancy. If so, determination of the time of onset of some change in the character of uterine souffle

will serve auscultatory notice that uterine conversion is accomplished. And it will tell the obstetrician that from that time hence, each week of intrauterine life is a week toward viability.

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SICKLE CELL ANEMIA AND PREGNANCY

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AT LEAST 33 cases of sickle cell anemia associated with pregnancy have been reported in the literature.[1-20] The maternal and fetal mortality figures may be summarized as follows:

Number of mothers	33	
Number of maternal deaths	7	(21 per cent)
Total number of pregnancies	73	
Total number of abortions	14	(19.1 per cent)
Total number of viable infants	59	
Number of infants surviving	50	
Deaths of viable infants	9	(15.2 per cent)
Total fetal loss in 73 pregnancies	23	(31.5 per cent)

The seven maternal deaths which have been reported in cases of sickle cell anemia associated with pregnancy are summarized in Table I. Infections, peripheral vascular collapse, thrombosis with embolic phenomena, and cardiac failure were the main causes of death. The clinical courses of three of the seven fatal cases were complicated by toxemia of pregnancy. In these fatal cases, as well as in many others in the total series, prenatal care was lacking, and in a few instances the patient received her first medical care when in moribund condition. This was illustrated in the case described by Lash[2] in which the patient had been in labor for fifty-two hours with a conjugata vera of 8 cm., and belated cesarean section was followed by death of the patient six hours later. The autopsy pointed toward a "shock" type of death.

The weights of the organs in the seven fatal cases were of special interest. Two patients had spleens weighing 20 and 35 Gm. as evidence of the atrophy which occurs with sickle cell anemia, while two other spleens were tremendously enlarged, weighing 740 and 960 Gm. each. The heart weights were also slightly over the average, weighing 379, 420 and 390 Gm.

The cases of Bauer[21] and Tomlinson[22] should be mentioned as possible cases to be included in this review, but because of controversial points were not incorporated in our tables. Tomlinson,[22] in a review of a large series of cases of sickle cell anemia, described the case of a 23-year-old British West Indian woman dying of postpartum septicemia, but the author himself raised the question as to whether sickle cell anemia played any role in the cause of death. This was also true in the case described by Bauer[21] of a 20-year-old Negro woman who died in the fifth month of pregnancy with the cause of death as pelvic thrombophlebitis, with multiple pulmonary infarcts and macrocytic anemia of pregnancy. Microscopic section of the spleen showed sickle cells in the reticulum and severe sidero-fibrosis. Whether this case should be classified as macrocytic anemia of pregnancy or as sickle cell anemia with pregnancy could not be decided by Bauer.[21] Numerous authors[2, 4, 5, 7, 12, 15, 16] have reported the presence of the sickling phenomenon in the infants born of these thirty-three mothers. Twenty-one infants have been examined and eleven (52.4 per cent) were found to be positive for the sickle cell trait.

TABLE 1. SUMMARY OF THE LITERATURE OF DEATHS OCCURRING IN CASES OF SICKLE CELL ANEMIA ASSOCIATED WITH PREGNANCY

AUTHOR	AGE	CLINICAL COURSE	WEIGHTS OF ORGANS (GM.)				AUTOPSY CAUSE OF DEATH
			HEART	SPLEEN	LIVER	KIDNEYS	
Yater and Mollari[1] (1931)	25	Died 3½ weeks after a spontaneous abortion (27th week) "Abdominal crisis"	379	35	2090	366	Sickle cell anemia; old infarcts of spleen and kidneys; hypertrophy and dilatation of heart; "abdominal crisis"
Lash[2] (1934)	21	Died 6 hours after cesarean section after prolonged labor, uterine inertia 52 hrs. with obstetrical conjugate 8 cm. and 3,225 Gm. infant. Entered hospital c̄ hypertension	–	960	2420	330	Widespread dilatation and engorgement of capillaries of lungs, kidneys, liver, and spleen. (Postoperative shock.) Sickle cell anemia
Killingsworth and Wallace[5] (1936)	28	No data. Died 6 weeks postpartum	–	–	–	–	Puerperal infection
Page and Silton[8] (1939)	20	Died 22 hours after admission in 24th week of pregnancy. Diagnosis: bronchopneumonia	420	20	–	490	Pulmonary embolism with multiple infarcts of the lungs. Thrombophlebitis, pelvic veins. Sidero-fibrosis of the spleen
Kobak, Stein, and Daro[9] (1941)	22	Died 6 hours after delivery of a full-term infant. Treated for right lower lobe pneumonia	–	–	–	–	Sickle cell anemia. Marked hepatosplenomegaly. Atelectasis and passive congestion, lower lobe of left lung. Parenchymatous changes in heart
Noyes[13] (1946)	32	Died undelivered in 28th week of pregnancy. Elevated blood pressure 170/100 with silver wire changes in retina. Toxemia	390	740	2030	–	Sickle cell anemia. Right sided heart failure. Visceral congestion
Carangelo and Otts[17] (1947)	20	Died 12 hours after delivery in 36th week of pregnancy. Edema and blood pressure 140/75. Temperature 103° F.	–	225	2170	–	Bilateral renal abscesses and overwhelming kidney infection

Present Study

As may be seen from the above review, previous experience with sickle cell anemia in pregnancy indicates that both the maternal and fetal prognosis is grave. Since our experience at the Johns Hopkins Hospital with sickle cell anemia associated with pregnancy—eleven cases with no maternal deaths—permits a more sanguine outlook than has hitherto been indicated, it seemed desirable to report our observations.

During the period from 1927 to 1947, eleven cases of sickle cell anemia associated with pregnancy have occurred on the obstetrical service of the Johns Hopkins Hospital. During this period, 14,256 Negro women were delivered in this hospital. This is an incidence of 1 in 1,296 pregnant Negro patients. Diggs, Ahmann, and Bibb[23] found that the incidence of the sickle cell trait was 7.3 per cent in 8,453 Negroes and that 1 in 40 Negroes with the sickle cell trait had active sickle cell anemia. From their data, approximately 1 in 552 nonpregnant Negroes would have sickle cell anemia and therefore our incidence of 1 in 1,296 pregnant Negro patients would lend some support to the generally accepted belief[7] that sickle cell anemia is associated with decreased fertility.

Our criteria for the diagnosis of sickle cell anemia have been the generally described ones of Wintrobe,[24] namely, marked anemia, evidence of red blood cell regeneration as shown by nucleated red blood cells in smears, elevated icteric index and jaundice with marked sickling of the red blood cells in carefully prepared sickling preparations. It should be re-emphasized that the single finding of "sickling" of red blood cells does not make the diagnosis of sickle cell anemia. In our eleven cases summarized in Table II, the diagnosis of sickle cell anemia was established on the following points:

1. Anemia, values usually under 50 per cent hemoglobin.
2. History, abdominal and joint pains, jaundice, weakness, dyspnea.
3. Examination, asthenic habitus, leg ulcers, cardiac enlargement with systolic murmur.
4. Sickling preparations, immediate sickling of the red blood corpuscles, with 80 per cent or more showing sickling after a twenty-four-hour period.
5. Icteric index, varied from 10 to 30.
6. Blood smears, reticulocytes, nucleated red blood cells frequently encountered in Wright's stain preparations of the blood.

Very little emphasis has been given to the association of syphilis and sickle cell anemia but for matter of record 7, or 63 per cent, of our cases either had positive serology or had been previously treated for syphilis. The significance of this observation cannot be determined. In all cases the diagnosis of sickle cell anemia was made during the prenatal period and in addition all cases were admitted to the hospital for treatment and study during their pregnancy. The average total hospital stay was 35 days, of which 23 were antepartum days and 12 postpartum days. The age of the patients was compatible with the previous literature in which only three of thirty-three cases occurred in women more than 30 years of age. Likewise, the parity of our patients was low since only seventeen pregnancies occurred in eleven mothers and only one mother had had a previous viable or full-term infant.

The prenatal course of the patients was not always tranquil. As may be seen in Fig. 1, the degree of anemia present in some cases was extreme, with four patients showing hemoglobin values under 40 per cent. Whole blood transfusions were given to ten of the eleven patients during the period of gestation and immediate puerperium. The average amount of blood administered in these ten cases was 2,650 c.c. and the average number of transfusions per patient was 5.2. In one case it was necessary to give nine transfusions over a period of

TABLE II. CASES OF SICKLE CELL ANEMIA AND PREGNANCY AT THE JOHNS HOPKINS HOSPITAL SINCE 1925

CASE	YEAR	AGE	PARA-GRAV.	HB. %	DELIVERY	BLOOD LOSS C.C.	MATERNAL OUTCOME	FETAL WEIGHT (GM.)	FETAL OUTCOME	SICKLING IN BABY	REMARKS
1	1927	21	0-1	21	Spontaneous	900	Well at 6 weeks	1,150	Died of prematurity		Labor induced because of anemia and cerebral thrombosis
2	1928	21	0-1	26	Low forceps	150	Alive	3,165	Alive		No follow-up
3	1938	27	0-1	30	Hysterotomy, 18 weeks		Died 2 years postpartum	200	Abortion		Chronic glomerulonephritis
4	1939	18	0-2	35	Low forceps	100	Well at 4 years	2,560	Alive	Negative	Tubal ligation 38th day postpartum because of feeblemindedness
5	1945	20	0-3	62	Spontaneous	25	Well 2 years later	2,860	Alive	Negative at 2½ years	Gross hematuria from hemorrhagic cystitis
6	1945	17	0-1	50	Spontaneous	300	Well 2½ years later	2,120	Alive	Negative at 2½ years	
7	1946	29	0-1	55	Spontaneous	250	Well at 6 months	1,950	Died of prematurity		Severe pre-eclampsia
8	1946	23	0-1	48	Spontaneous	50	Well at 1 year	2,560	Alive	Negative	
9	1947	20	0-1	60	Breech, spontaneous	250	Well at 6 months	2,860	Alive	Negative at 3 months	
10	1947	23	0-1	62	Forceps rotation	500	Well at 6 months	3,370	Stillborn		Occipitoposterior position rotated to occipitoanterior
11	1945	20	3-4	50	Spontaneous	100	Well at 2 years	2,940	Alive		Mild pre-eclampsia

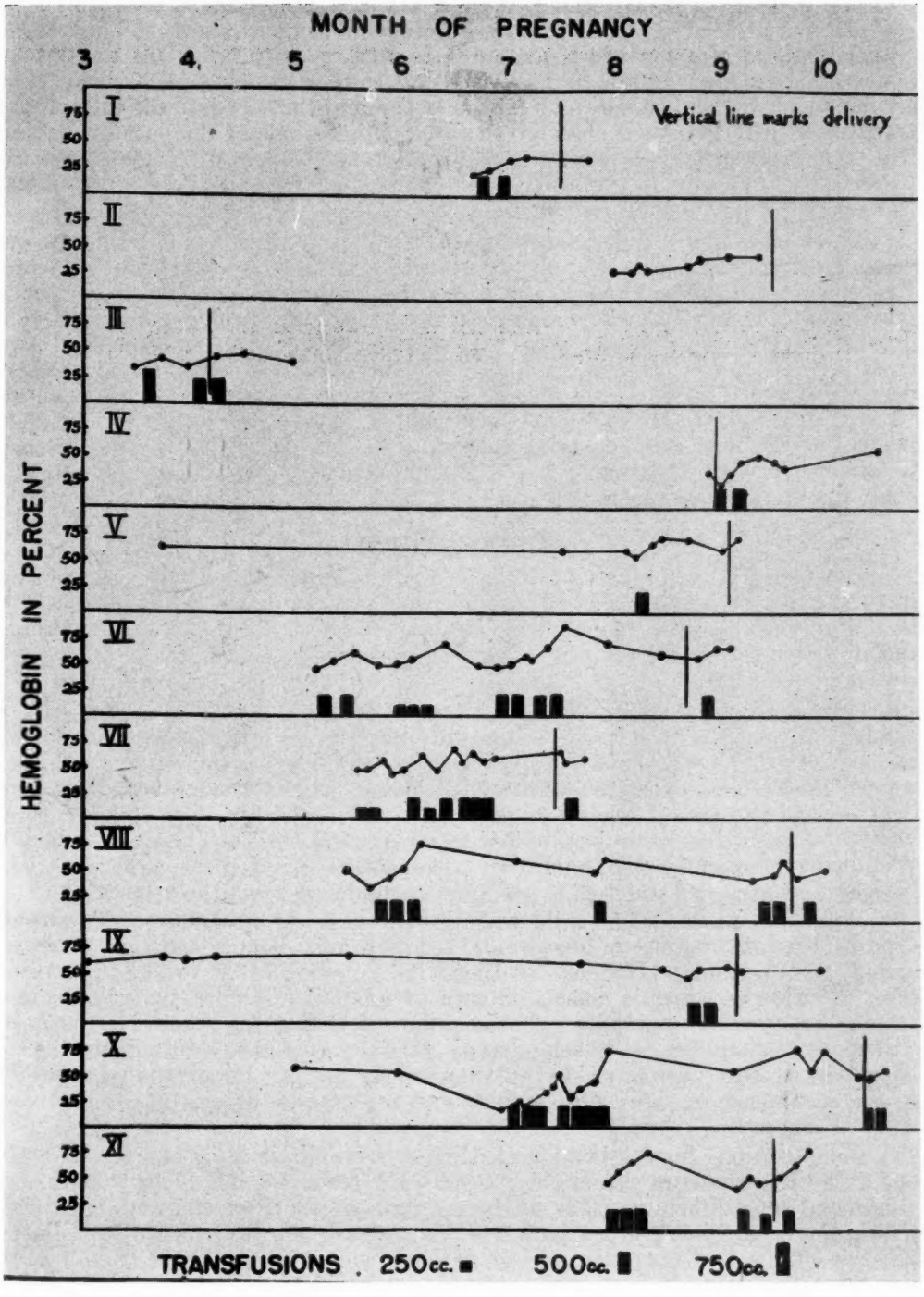

Fig. 1.—Hemoglobin values and blood transfusions administered to eleven cases of sickle cell anemia in pregnancy.

fourteen weeks in order to maintain the hemoglobin values at a satisfactory figure. In fifty-two transfusions recorded in Fig. 1, twelve transfusion reactions (23 per cent) occurred. Eleven of the reactions were the simple febrile reactions with chills and temperature rises to 101 to 102° F. within one to twenty-four hours after administration of the blood. One reaction was of a severe type accompanied by abdominal pain and hemoglobinuria. Practically all of the transfusion reactions were observed in three patients, one of the patients having five transfusion reactions. In several instances differences of opinion were expressed by members of the staff as to whether the reactions were abdominal "crises" or simple transfusion reactions.

Febrile reactions, independent of simple febrile transfusion reactions, developed during the prenatal and postpartum intervals in several of our patients. Pyelitis was present in three cases, meningitis in 1, and an unexplained febrile reaction in another, to make a total of five cases in which febrile reactions were present during the gestation period. Likewise, in the postpartum period, two cases of episiotomy infection, and single cases of brain abscess and pyelitis developed, which make a total of nine instances in which febrile reactions necessitated hospitalization and liberal treatment with bed rest, sulfonamides, and penicillin. In one patient, leg ulcers of considerable size were troublesome, requiring prolonged bed rest. The usual stasis edema of pregnancy adds to the delay in healing these ulcers.

Hemolytic Crises

Hemolytic crises occurred in only one case during pregnancy (Case 9) and in three cases (Cases 3, 4, and 9) during the postpartum period. Although there is a wide variation in the frequency of "crises" in cases of sickle cell anemia, certainly one crisis during the period of gestation is a minimal number for eleven pregnancies.

Only one instance of a thrombotic process was observed. In this case a cerebral thrombosis took place similar to that seen in a pregnant woman described by Hodges and Bernstine[16] and to the observations in nonpregnant women by Hughes, Diggs, and Gillespie,[25] Connell,[26] and Bridgers.[27] This accident occurred in Case 1 two weeks before delivery. Because of anemia and cerebral thrombosis the labor was induced and a 1,150 Gm. infant was delivered, who died subsequently of prematurity. The mother survived the cerebral thrombosis and abscess and was well at the time of discharge from the hospital.

Three of our cases had mild to severe toxemias of pregnancy. The usual type of toxemia regime with bed rest, sedation and dietary control prevented serious complications. Hodges and Bernstine[16] observed that two of their three cases of sickle cell anemia associated with pregnancy developed signs and symptoms of toxemia of pregnancy. These authors feel that the arteriolar spasm of toxemia superimposed on vessels already partially occluded by the intimal proliferation which occurs in sickle cell anemia may bear an important relationship to the occurrence of signs and symptoms of thromboses, especially cerebral vascular blockage.

Complications during labor and delivery were minimal in our cases. Only one case of postpartum hemorrhage (900 c.c.) occurred, but blood transfusion eliminated any difficulty. The average length of the first stage of labor was fifteen hours and the average second stage was one hour and forty-five minutes. In view of the fact that most of our patients were primigravidas, these figures approach the normal; however, the average duration of the second stage was somewhat protracted and in one case was three hours long. The pelvic factor in these cases will be considered later.

We were able to study the placentas microscopically in only six of our cases. No abnormalities of fetal-placental weight ratios were observed. In two of the six placentas sickling of the red blood cells of the maternal blood was present (Fig. 2) but in no instance did we observe sickling of the fetal blood cells. Five of the eleven infants were also studied for sickling, but in no case was sickling demonstrable at the time of birth.

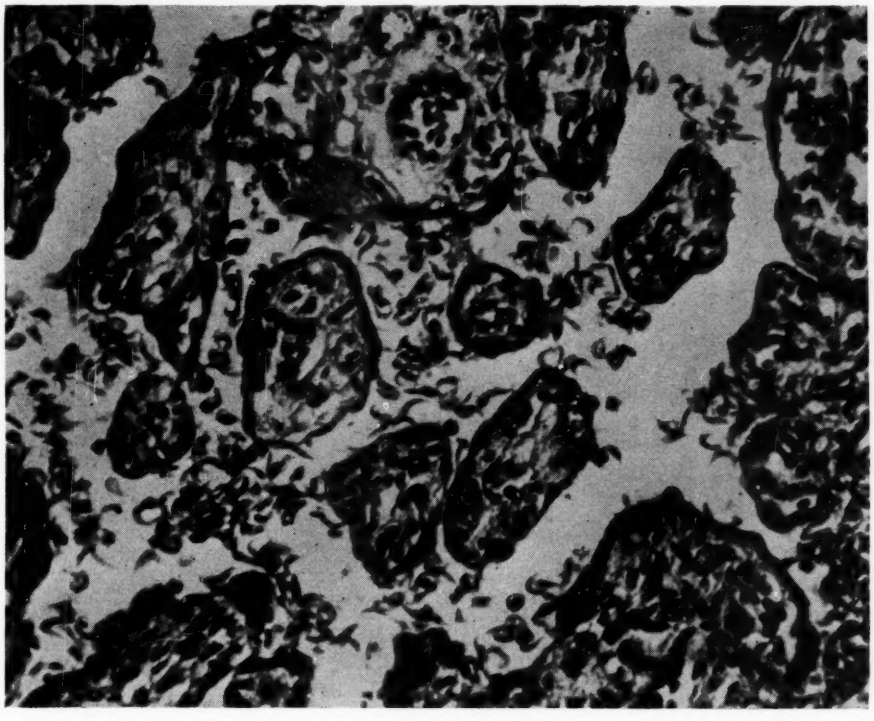

Fig. 2.—Placenta from Case 4 showing massive sickling of blood in the maternal sinuses. Note that the blood in the fetal vessels shows no evidence of sickling.

The fetal and maternal results are shown in Table II and summarized as follows:

Number of mothers	11	
Number of maternal deaths	0	(0 per cent)
Total number of pregnancies	17	
Total number of abortions	4	(23.5 per cent)
Total number of viable infants	13	
Number of infants surviving	10	
Deaths of viable infants	3	(23.1 per cent)
Total fetal loss in 17 pregnancies	7	(41.2 per cent)

The mortality rate of viable infants (over 1,000 Gm.) in our series (23.1 per cent) is not encouraging. However, closer analysis of Table II shows that in the three deaths of viable infants one case was due to induction of a small premature (Case 1) because of a severe cerebral thrombosis in the mother. The second death was in Case 7 which was associated with severe pre-eclampsia. The third death, the only one in a full-term infant, occurred after injudicious forceps

rotation in a type of pelvic architecture in which rotation is unwise. As also can be seen in Table II, not one of our patients died during pregnancy or the puerperium; however, one patient (Case 3) died two years after her pregnancy of chronic glomerulonephritis. To our knowledge (and with the exception of one case, postpartum follow-up at six weeks to four years was obtained on all our cases) this is the only death in the eleven cases.

Interesting features of the sickle cell anemia patient which should be of interest to the obstetrician are the changes in the bony structure and habitus of these patients. Winsor and Burch,[28] Sharp and Vonder Heide[29] have described these alterations in detail. They maintain that the sickle cell anemia habitus depends upon the extent and duration of the disease and the age of the patient at the time of onset. The sickle cell habitus was described as linear; the subjects were underweight, the hips and shoulders were narrow and the stature decreased. An increased upper dorsal kyphosis and lumbar lordosis and an increase in the anteroposterior diameter of the chest (''hoop chest'') were characteristic with short trunks and roentgenologic evidence of flattening of the lumbar vertebrae. A few external measurements of the pelves were made in these studies but no mention of the obstetrical capacity of the pelves was included.

TABLE III. X-RAY PELVIMETRY IN FOUR CASES OF SICKLE CELL ANEMIA

	INLET		MIDPELVIS			OUTLET			
CASE	O.C.	T.D.	I.S.	THOMS P. S.	A.P.	T.I.	P.S.	MORPHOLOGY	REMARKS
5	11.0	11.0	9.3	4.6	12.2	9.0	8.3	Gynecoid-anthropoid	Convergent side walls. Straight sacrum
6	11.2	13.6	9.2	3.8	11.0	7.6	8.4	Gynecoid with anthropoid outlet	Convergent side walls. Straight sacrum
9	10.8	13.0	9.6	3.4	11.2	10.2	6.6	Gynecoid	Crests not united
10	12.3	12.9	9.2	4.0	11.6	9.6	5.3	Android-anthropoid	Straight sacrum. Convergent side walls

In view of the above observations, all patients who could be traced were measured. In three of 5 pelves measured by clinical pelvimetry, outlet contraction was found to be present (intertuberous diameter of less than 8.0 cm.). In two other cases a diagonal conjugate of less than 11.5 cm. was discovered. Because of the known variations in estimation of obstetric capacity by clinical mensuration, x-ray pelvimetry was obtained on four patients and the data tabulated in Table III. From this table it will be noted that three of the four pelves had convergent side walls, with heavy, blunted ischial spines. In Fig. 3, two of the pelves have been illustrated with anteroposterior and lateral x-ray views to show the straight sacra with no forward rotation as is characteristic of kyphoscoliosis. The arches are narrow but not composed of heavy bony structure; otherwise they resemble the anthropoid type of pelvic architecture. Case 10 (Fig. 3) illustrates an instance in which a full-term infant was lost at the time of delivery by an ill-advised forceps rotation in a contracted outlet. Case 6 has a very small transverse diameter of the outlet (7.6 cm.) but fortunately the patient delivered a premature infant weighing only 2,120 grams. The type of pelvic architecture associated with sickle cell anemia habitus could very well be the reason for some of the difficult labors and prolonged second stage difficulties which are described in the previous literature.

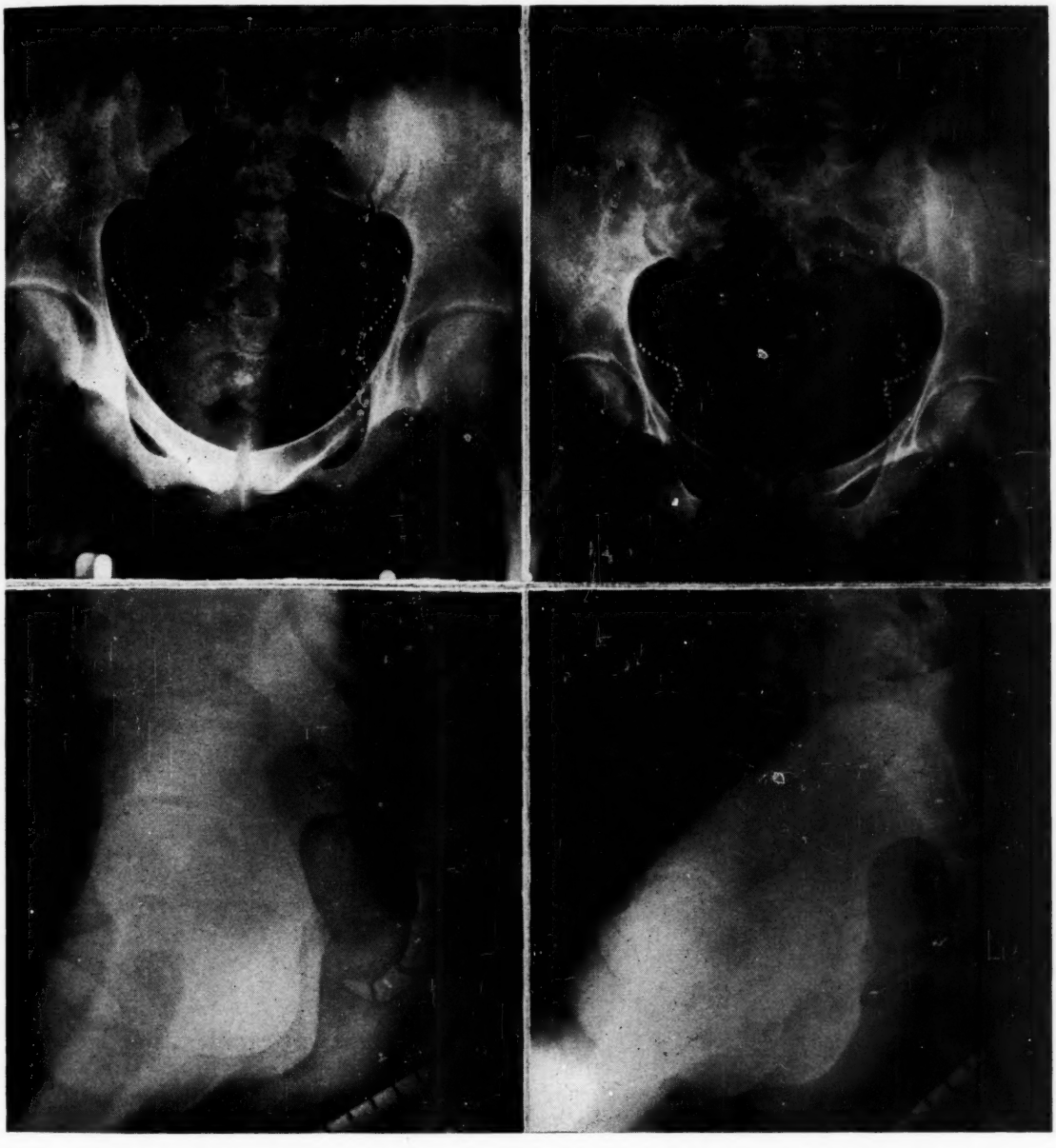

Fig. 3.—X-ray pelvimetry in Cases 10 and 6. On the left, an android-anthropoid pelvis of poor obstetrical type is demonstrated. On the right, a gynecoid pelvis with an anthropoid outlet and straight sacrum is shown.

Treatment

The patients observed in the present study extend over a 20-year period (1927-1947). During this same interval, many new therapeutic developments such as antibacterial substances and blood transfusion have been added. Therefore, a plan of therapy should be outlined for cases of sickle cell anemia associated with pregnancy in the light of present knowledge and chemotherapeutic developments. Since the largest number of deaths from sickle cell

anemia both in pregnant and nonpregnant patients are due to intercurrent infections, cardiac and renal failure, shock and allied peripheral vascular changes, the treatment program should be directed primarily at the prevention of these accidents.

During the prenatal period sickle cell anemia patients should be observed frequently and if abdominal pains, febrile reaction, excessive weight gain, lowered hemoglobin values, hypertension, albuminuria, pyuria, or hematuria develops, the patient should be hospitalized immediately. Careful physical examination and hematological investigation should be performed. If fever is present, sources of infection should be sought and an attempt made to establish the bacteriologic etiology. Various combinations of penicillin or sulfonamide therapy should be instituted depending upon the sensitivity of bacterial organism in each individual case. During labor and the immediate puerperium it is wise to use penicillin in doses of 200,000 to 300,000 units. This step is advocated because of the high incidence of puerperal infection and morbidity, not only in cases of sickle cell anemia but also in all cases of anemia in pregnancy. Should early rupture of membranes occur. the prophylactic use of penicillin may be instrumental in protecting both mother and fetus from invasion by bacteria.

As has been previously discussed and illustrated in Fig. 1, we have used transfusions of whole blood liberally, with the average number of transfusions per case 5.2. Although the effect of the transfusions as measured by hemoglobin determinations is often temporary, certain beneficial effects appear to have been obtained rather than the mere increase in hemoglobin. It is true that the value of blood transfusions in sickle cell anemia patients in general has been debated. In nonpregnant patients, many authorities, such as Wintrobe,[24] consider them of little or no value. Bauer[21] and Tomlinson[30] have pointed out single instances in which transfusions may have had a deleterious role, while Tomlinson[30] has described the dangers that could be encountered if blood donors with sicklemia are used. Except for the one patient in the present study, no such difficulties were observed.

To obstetricians, however, there may be other arguments in defense of the use of transfusions in the pregnant patient with sickle cell anemia. The presence of any type of anemia associated with gestation is a frequent precursor of future difficulties in the period of labor and the puerperium. Pastore[31] and Bickerstaff[32] have conclusively shown that puerperal morbidity is in direct proportion to the degree of anemia present in pregnant patients. As has been pointed out in the review of the literature, toxemias frequently accompany sickle cell anemia during pregnancy. The recent studies of Hinselmann,[33] Linzenmeier,[34] and Krogh[35] establish the basis for "stasis" within the fingernail capillaries of normally pregnant and toxemic patients. Knisely and Bloch[36] have made studies of intravascular agglutination occurring in normal, experimental, and pathologic states. One of the conditions in which they observed an increase in microscopic agglutination of red blood cells in venules and arterioles was sickle cell anemia. Recently, Odell and his co-workers[37] have found this "sludging" effect to be present in normal and pathologic pregnancy. Odell[37] also concludes that during shock sludge is related to subsequent hemodilution, or to the accompanying operative trauma rather than to an acute loss of blood. During infection, thrombophlebitis, and pre-eclampsia, the size of intravascular masses is particularly increased. What relationships do these alterations of pregnancy have in regard to the pathological physiology of sickle cell anemia?

The earlier workers with sickle cell anemia, such as Mason,[38] felt that hemolysis in sickle cell anemia was caused by phagocytosis of defective erythrocytes by macrophages with liberation of hemoglobin. Later on, Bauer[39] introduced the idea that simple mechanical impaction of masses of deformed red blood cells in small blood vessels was responsible for the hemolysis. Bauer[39] concluded

that the essential pathologic process in sickle cell disease was stagnation and conglutination of disfigured red blood cells with the resultant processes of thrombosis, ischemia with necrosis and fibrosis, and the resolution of red blood cells with the subsequent development of anemia. Recently, Ham and Castle[40] have developed the idea of an "erythrostasis" which enhances hemolysis. These authors have observed that sickling blood has a higher viscosity which predisposes to erythrostasis. Tomlinson,[22] in a study of eleven cases of nonpregnant "abdominal crises" which resulted in death, suggested that the mechanism of death was shock. His explanation of the shock was that the anoxia accompanying anemia was increased in sickle cell anemia because the sickled erythrocytes are poor carriers of oxygen to body tissues. The heart, as studied by Klinefelter,[41] is weakened in sickle cell anemia. The capillary anoxia results in plasma loss, hemoconcentration stagnation, and the stagnation removes available erythrocytes from the circulation, increasing the circulatory failure and anoxia, which perpetuates the vicious cycle of shock. Tomlinson,[22] therefore, feels that transfusions must be given in sickle cell anemia, particularly in the presence of "crises." In addition to the alterations of the maternal physiology which would enhance the difficulties in treatment of the anoxia of the mother, the exchange of oxygen between mother and fetus must be maintained. With these points in mind, transfusions would appear to be indicated in the mother with sickle cell anemia. It is also advisable to use sodium lactate solutions along with whole blood to prevent not only renal complications but possibly also to reduce the sickling tendency by raising the pH of the blood. Altmann[42] attempted to determine the fate of transfused erythrocytes in sickle cell anemia and concluded that the hemolytic process in sickle cell anemia affects only the patient's own red blood cells which are abnormal due to some hereditary factor, while the transfused cells remain unaffected.

Reinhard and his co-workers[11] have tried the effects of high concentrations of inspired oxygen on patients with sickle cell anemia. With the exception of a decrease in the degree of intravascular sickling of red blood cells, no consistent change in the rate of hemolysis occurred during the period of oxygen administration. Only minor toxic manifestations developed during the periods of oxygen therapy. Although no great benefits were derived from oxygen therapy, it should be pointed out that in patients with sickle cell anemia congestive heart failure which does not respond to digitalis has been reported by Klinefelter.[41] It may be necessary during pregnancy to use oxygen therapy since there is an increasing circulatory burden on the normal pregnant patient's heart, and this alteration on an already affected cardiac function in sickle cell anemia patients would be very serious. Therefore, the patients with sickle cell anemia with pregnancy should receive treatment closely resembling the type given patients with valvular heart disease.

The question of anesthesia is difficult, but the advent of various types of block anesthesia offers some advantage over inhalation anesthetics such as nitrous oxide and oxygen alone or combined with ether; this is particularly important in regard to the fetal outcome. Everything done to prevent circulatory stasis is advantageous in the treatment of patients with sickle cell anemia and pregnancy. Bauer[39] suggests sufficient muscular exercise, avoidance of prolonged bed rest, thyroid extract, cool baths, and saline and dextrose infusions to prevent circulatory stagnation.

In the previous discussion we have indicated our optimistic attitude that with appropriate medical and obstetrical care patients with sickle cell anemia can be safely carried through pregnancy. However, one of the problems confronting the obstetrician is the question of therapeutic abortion and sterilization in women afflicted with sickle cell anemia. Textbooks of hematology[24, 38, 43] state that sickle cell anemia is a hereditary disease transmitted as a Mendelian

dominant factor. Closer analysis of the literature as to the source of this conception shows that it apparently originated with Huck[44] and Sydenstricker.[19] Huck[44] studied two families for three generations and found that the "sickling" phenomenon is transmitted in this manner. His data and charts are only concerned with the sickling trait and therefore are insufficient evidence to conclude as he did, that sickle cell anemia is also hereditary. Mason[38] stated that proof of the statement that sicklemia invariably precedes the development of sickle cell anemia is still a matter of debate. Lewis[45] also believes that the relationship of the disease sickle cell anemia to the sickle cell trait is a matter of controversy. It is important to point out that some authors like Murphy and Shapiro[46] feel that the anemia differs from the trait only in a matter of degree. This viewpoint is also shared by Bauer[39] who feels that the anemia is a secondary condition and that sicklemia may be converted to active sickle cell disease by some acute infectious disease or surgical procedure. Even if one were to consider every person with the sickling trait a potential case of sickle cell anemia, the figures of Diggs et al.[23] would indicate that only one in forty patients with the trait develops anemia. Apparently no way has been devised to predict the cases of sicklemia which will develop the acute phase of the disease.

As yet the prognosis of children born to mothers with active sickle cell anemia cannot be stated with assurance. A thorough search of the literature revealed only two reports (Killingsworth and Wallace[5] and Corrigan and Schiller[20]) in which the true picture of sickle cell anemia has been observed in both the mother and her children. Until more data have been accumulated, conclusions cannot be made as to whether an infant born of a mother with sickle cell anemia is more likely to develop this disease than an infant born of a mother with only the sickling trait. Therefore, therapeutic abortion for sickle cell anemia alone would not be justified. Sterilization will rarely be necessary since patients with sickle cell anemia have an average number of only two pregnancies and some 20 per cent of the pregnancies terminate in abortion. However, many other factors may govern these recommendations. Bauer[39] has advanced the idea that patients with sickle cell anemia belong to a group characterized by constitutional degenerative stigmas which he designates as the "status degenerativus." From the reports in the literature the clinician must be on guard against many treacherous and peculiar mechanisms which initiate "sudden death" in patients with sickle cell disease. Each case must be given individual consideration. For instance, an associated toxemia of pregnancy with sickle cell anemia could alter one's decision regarding interruption of pregnancy and future childbearing.

Discussion

The high maternal mortality rate of 21 per cent reported in the previous literature could not be corroborated in the present study of eleven cases of sickle cell anemia associated with pregnancy observed in the Obstetrical Department of the Johns Hopkins Hospital over a 20-year period (1927-1947). All patients survived the period of the pregnancy and puerperium. Follow-up on the patients extended from six weeks to four years in the present study. In Table IV, a summary of the previous literature, the present study, and the combined total of forty-four cases are presented. From these data the total fetal loss and abortions appear to be increased over normal. Our percentage of deaths of viable infants (over 1,000 Gm.), 23.1 per cent, is higher than the figure of the previous literature, 15.8 per cent, but two of the deaths in the present study and some of the reported fetal deaths suggest ill-advised obstetric and pediatric procedures.

With improved methods, there is every reason to believe that a fetal mortality rate of 5 to 10 per cent may be attained.

TABLE IV. SUMMARY OF MATERNAL AND FETAL MORTALITY OF CASES OF SICKLE CELL ANEMIA IN THE LITERATURE AND IN THE PRESENT STUDY

	PREVIOUS LITERATURE		AUTHORS' CASES		TOTAL CASES	
	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT
Number of mothers	33		11		44	
Number of maternal deaths	7	21.0	0	0	7	15.9
Total number of pregnancies	73		17		90	
Total number of abortions	14	19.1	4	23.5	18	20.0
Total number of viable infants	59		13		72	
Total number of surviving infants	50		10		60	
Deaths of viable infants	9	15.2	3	23.1	12	16.6
Total fetal loss	23	31.5	7	41.2	30	33.3

Sickle cell anemia should be looked for in obstetrical services handling Negro patients. Practically all of our cases had the diagnosis of this disease established while under the care of the obstetrical staff. Therefore, the routine testing of Negro patients for hemoglobin values followed by sickle cell diagnostic tests should be a part of the function of the prenatal clinic. Blood donors probably should also be checked for sicklemia as suggested by Tomlinson.[30] It is often stated that sickle cell anemia is easily diagnosed but in the present study three cases, which had been recorded in the files as sickle cell anemia, had to be rejected because insufficient evidence was present to establish clearly this diagnosis. None of these patients died and only the sickling trait was present with moderate anemia. One patient had tuberculosis, another rheumatic fever, and a third chronic pyelonephritis.

Summary

The present study is a review of eleven cases of sickle cell anemia associated with pregnancy observed on the Obstetrical Service of the Johns Hopkins Hospital over a 20-year period (1927-1947). No deaths occurred in these eleven mothers during the period of the pregnancy or puerperium. Three of thirteen viable infants died, giving a fetal mortality of 23.1 per cent. These figures justify a more optimistic outlook than hitherto noted in sickle cell anemia associated with pregnancy, since the previous literature reports an average maternal mortality rate of 21 per cent in thirty-three cases. Fifty-nine viable infants were born of these thirty-three mothers with nine deaths, giving a fetal mortality rate of 15.2 per cent.

Sickle cell anemia occurred in one in 1,296 pregnant Negro women. Repeated hospitalization during the prenatal period was necessary. The average number of transfusions per patient during the pregnancy and puerperium was 5.2. Twelve reactions occurred in fifty-two transfusions given these patients (23.0 per cent). Only single instances of thrombosis and abdominal crises were observed during the pregnancies. Three cases were complicated by toxemias of pregnancy. Analysis of eleven cases did not support the idea that pregnancy exerted an untoward effect on the disease of sickle cell anemia.

X-ray pelvimetry was studied in four cases, of which three had convergent side walls with heavy, blunted ischial spines. The pelves revealed a tendency toward funneling and anthropoid architecture with straight sacra and narrow subpubic arches. Further x-ray studies should be made.

The treatment of sickle cell anemia associated with pregnancy demands constant medical observation and frequent hospitalization for investigation and treatment of concurrent toxemias and febrile states. Liberal use of penicillin, sulfonamides, and blood transfusions is needed to reduce both the maternal and fetal mortality rates. With the addition of the present study to the thirty-three previously reported cases in the literature, a total of forty-four cases have been observed up to the present time. Seven maternal deaths (or 15.9 per cent) have occurred with a fetal mortality of 16.6 per cent and a total fetal loss of 33 per cent. Therapeutic abortion and sterilization are seldom indicated in patients with sickle cell anemia associated with pregnancy.

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THE EFFECT OF VERATRUM VIRIDE ON THE URINE VOLUME, BLOOD PRESSURE AND PULSE RATE IN NORMAL AND TOXEMIC PREGNANCY*

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DURING the last few years a new surge of interest in the treatment of the toxemias of pregnancy with veratrum viride has appeared in the literature. Bryant[1] and Bryant and Fleming[2] were the first among modern authors to report a significant series of cases of eclampsia treated by this drug with successful results and low maternal mortality. Garber and Assali[3] added 40 cases to the series of Bryant and Fleming, making a total of 160 eclamptic patients treated at the Cincinnati General Hospital with the same regimen, resulting in a gross maternal mortality rate of 1.8 per cent.† Kellogg[4, 5] and Irving[6] reported a decrease from 25 per cent to 12 per cent in their maternal mortality in eclampsia following the institution of veratrum viride therapy.

Willson[7, 8] published a series of cases of pre-eclampsia and hypertensive pregnancy wherein he found a decrease in the urinary output following the use of veratrum viride. He concluded that this drug should not be used in the treatment of eclampsia and pre-eclampsia because there was no necessity for lowering the blood pressure in these conditions. He postulated that the existing hypertension was actually beneficial for the maintenance of normal kidney function.

This is at variance with opinions expressed by Hertig[9] and others[10-11] who state that the predominant element in the toxemias of pregnancy is a generalized vasospasm, with resulting capillary anoxia and tissue necrosis.

Impressed by Willson's report, we initiated a clinico-experimental work designed to evaluate the action of veratrum viride on the urinary output of normal, toxemic, and hypertensive pregnancies. Blood pressure and pulse rate were also recorded in order to evaluate any possible correlation between these two factors and the urine volume. The results form the subject of this paper.

Material

Eight pre-eclamptic, two eclamptic, 3 hypertensive, and four normal pregnant patients comprised the present series. The duration of pregnancy varied from thirty-two weeks to full term. All of the patients were admitted to the hospital, kept at absolute bed rest, and placed on a 0.9 Gm. sodium chloride diet during the entire period of the experiment. Patients who were in active labor were eliminated because of the variation in blood pressure, pulse rate, and urinary output produced by labor pains. Of the eight cases of pre-eclampsia, six were severe and two mild. The diagnosis of pre-eclampsia was based on the presence of albuminuria, hypertension, edema, and subjective symptoms in the last trimster of pregnancy. One hypertensive, one eclamptic, and two pre-eclamptic patients were studied in the prepartum and postpartum period.

*Veratrum viride was employed in the form of Veratrone, Parke, Davis and Co.

†Since this last report, there have been 21 more eclamptic patients treated, a total of 181 cases with one maternal death from eclampsia per se and two from sepsis.

Method

Following admission, all patients were weighed and an indwelling Foley catheter inserted into the bladder; the first urine sample was discarded. The catheter was opened, thereafter, at hourly intervals and the bladder emptied completely each time. The present study was divided into three periods:

a. A control period varying from 8 to 48 hours. During this time the patient received measured amounts of water orally (100 to 400 c.c.). The urinary output, blood pressure, and pulse rate were recorded.

b. The period of veratrum viride administration, varying from 12 to 48 hours. It followed the control period immediately and consisted of the addition of subcutaneous doses of veratrum viride (0.2 to 0.7 c.c.) every two hours.

c. A combined period in which magnesium sulfate (50 per cent intramuscularly and glucose solution (5 per cent in distilled water) intravenously were added to the veratrum viride treatment.

This last method was applied to five pre-eclamptic and two eclamptic patients and it represented the treatment followed for more than twenty years in this hospital. In all of the periods intake, output, pulse rate, and blood pressure were recorded hourly or every two hours by the same observers to eliminate errors from personal variation. Since vomiting occurred frequently with large doses of veratrum viride, it was charted separately but was not included in the calculation of urinary output. Profuse sweating was observed frequently with large doses of this drug. It constituted, to a certain degree, a cause of error which could not be entirely avoided in calculating the output. To eliminate bed rest alone as a factor influencing diuresis and blood pressure, one pre-eclamptic and one hypertensive patient were studied in control periods alternating with veratrum viride. Urea clearance tests were performed at the end of each period using the Van Slyke method on three hourly specimens of urine and one of blood. Weight determinations were also recorded at the end of each period.

Results

A. *Normal Pregnancy.*—All of the four cases responded in the same manner to the administration of veratrum viride. With doses varying from 0.2 to 0.7 c.c.—the usual effective dose in treating pre-eclamptic patients—there was practically no change in the urine volume, blood pressure, or pulse rate. The urinary output maintained the same proportion during the control and veratrum viride administration periods (Fig. 1). Fig. 2 illustrates an individual example.

B. *Toxemias of Pregnancy.*—Under this heading were included the patients with pre-eclampsia and those with essential hypertension not showing any sign of superimposed toxemia.

1. *Urinary output:* In almost all of these patients, a decrease in the hourly urinary output (vomiting excluded) varying from 15 to 60 per cent was observed following the administration of veratrum viride. The mean decrease for the entire group was 37 per cent. The maximum drop in output occurred when larger doses (0.5 to 0.7 c.c.) were given and lasted for approximately two hours. It coincided with the sudden fall in blood pressure, profuse vomiting, and diaphoresis. However, with the return of the blood pressure to a desired level (circa 140/90) which was always lower than the control level, the urine volume increased and was so maintained even though the administration of veratrum viride was continued. Because of the compensatory polyuria which was observed frequently after the initial decrease in output, the total urinary output for the control and veratrum viride periods maintained almost similar proportions in all of the patients (Figs. 3, 4, and 5). The patients who were studied under the

combined regimen invariably showed increased urine volume despite the fact that the blood pressure and pulse rate were lower than in the control and veratrum viride periods (Fig. 4). The patients who were studied in the postpartum period had a marked diuresis in both control and veratrum viride

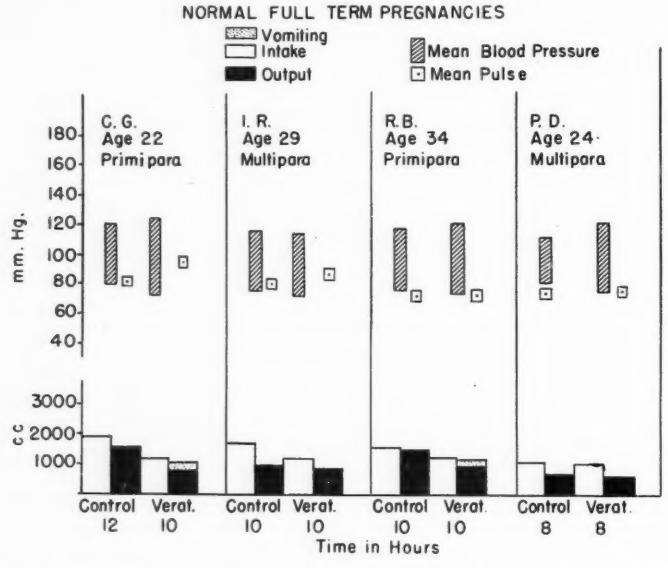

Fig. 1.—Total intake and output, mean blood pressure and pulse rate of four normal full-term pregnancies.

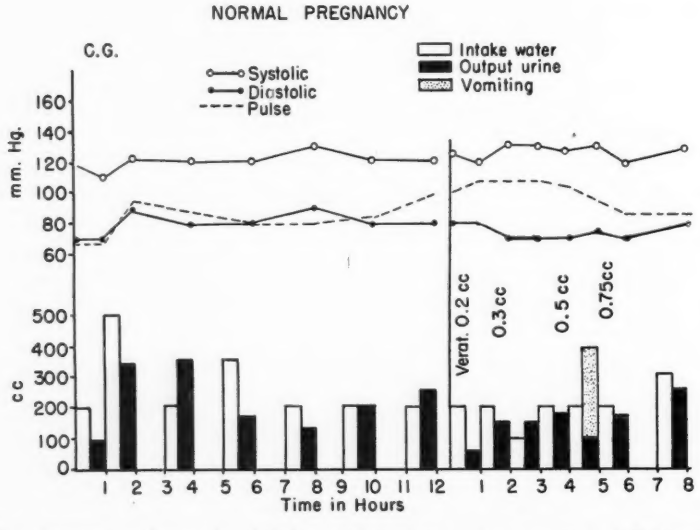

Fig. 2.—Blood pressure, pulse rate, intake and output of a normal full-term pregnancy in control and veratrum viride periods.

periods. Two patients were studied according to the alternating method mentioned above. In the prepartum, one of them (Fig. 6) showed a transitory decrease in urine volume each time veratrum viride was given in 0.7 c.c. doses. The other (Fig. 7) did not show any alteration. In the postpartum, both had profuse diuresis.

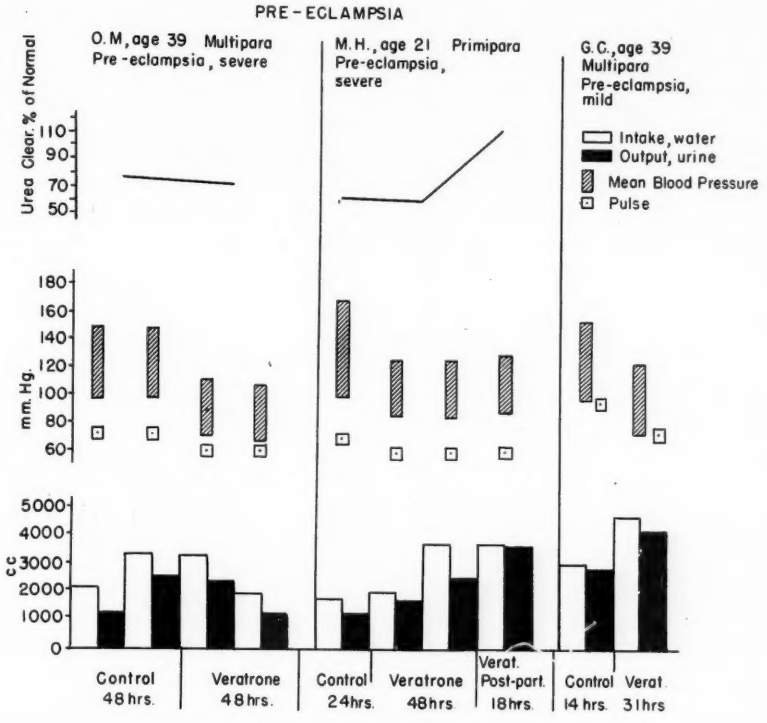

Fig. 3.—Total intake and output, mean blood pressure and pulse rate, and urea clearance of three pre-eclamptic patients studied on control and veratrum viride periods.

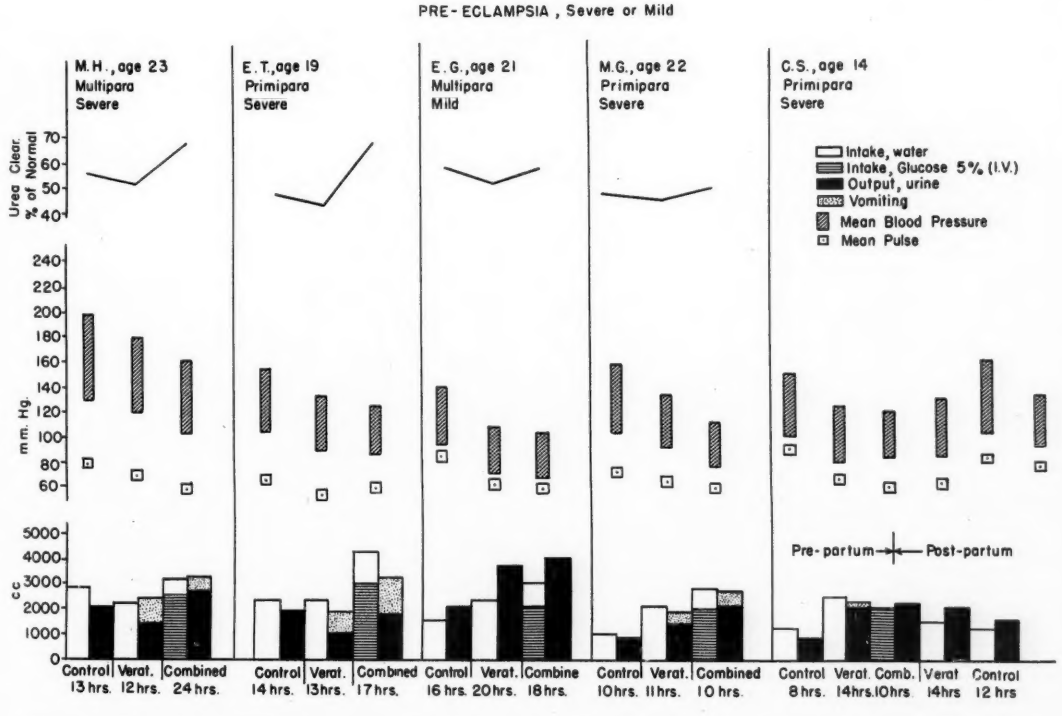

Fig. 4.—Total intake and output, mean blood pressure and pulse rate, and urea clearance variations in five pre-eclamptic patients during control, veratrum viride, and combined periods.

2. *Urea clearance:* This test was performed on six pre-eclamptic and two hypertensive patients. It showed some decrease following the veratrum viride administration but it returned to the original level or even higher during the combined period (Figs. 3, 4, 5). These oscillations in the urea clearance were considered within the range of variability usually attributed to this laboratory procedure.[12]

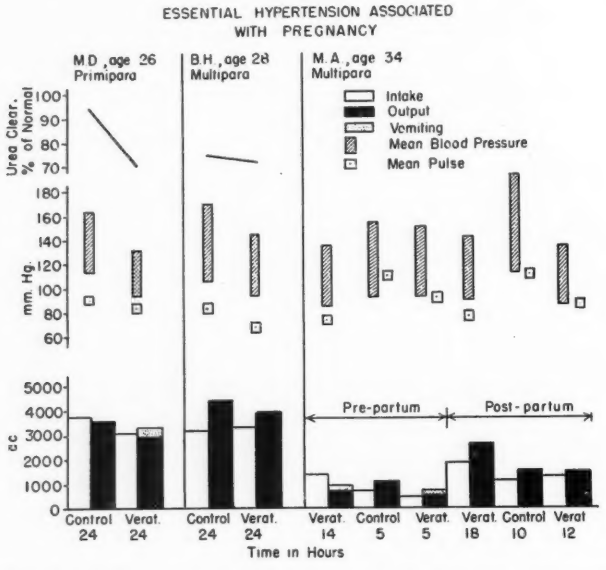

Fig. 5.—Total intake and output, mean blood pressure and pulse rate and urea clearance of the three hypertensive patients.

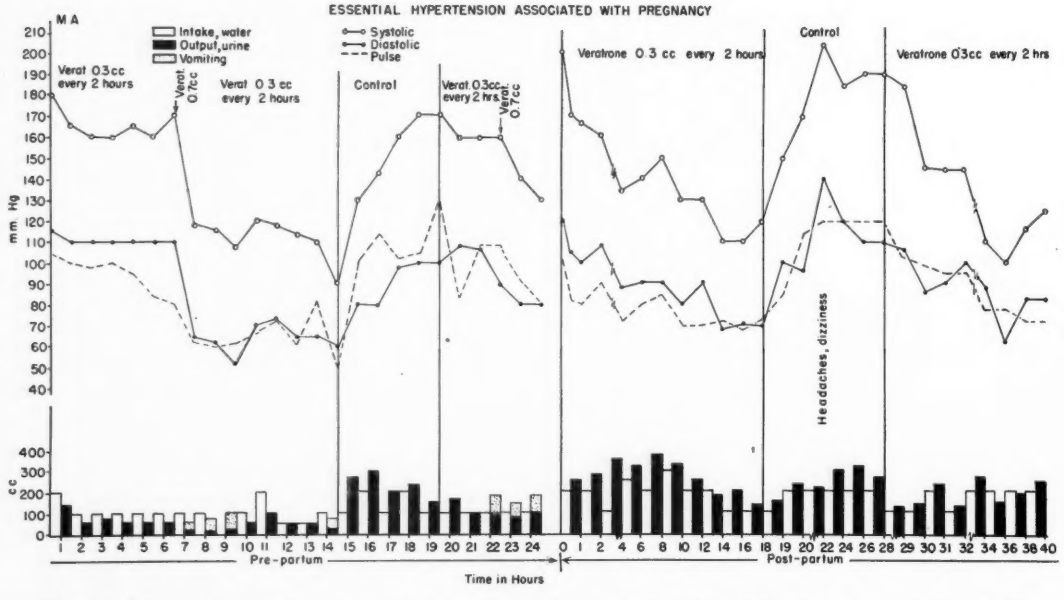

Fig. 6.—Alternating periods of control and veratrum viride administration in a patient with essential hypertension.

3. *Blood pressure and pulse rate:* In both pre-eclamptic and hypertensive groups the blood pressure and pulse rate were markedly decreased following the use of veratrum viride and paralleled each other. The greatest fall was 90 mm. Hg in the systolic and 60 mm. in the diastolic blood pressure. The lowest pulse rate recorded was 48.

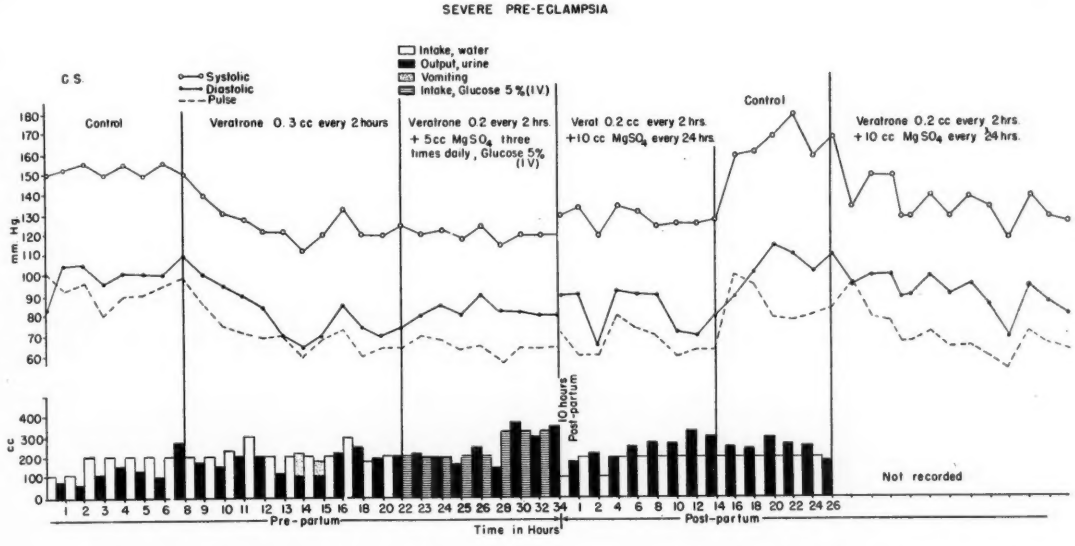

Fig. 7.—Alternating periods of control and veratrum viride administration in severe pre-eclamptic patient. Output in the last period was not recorded because the patient developed urethritis.

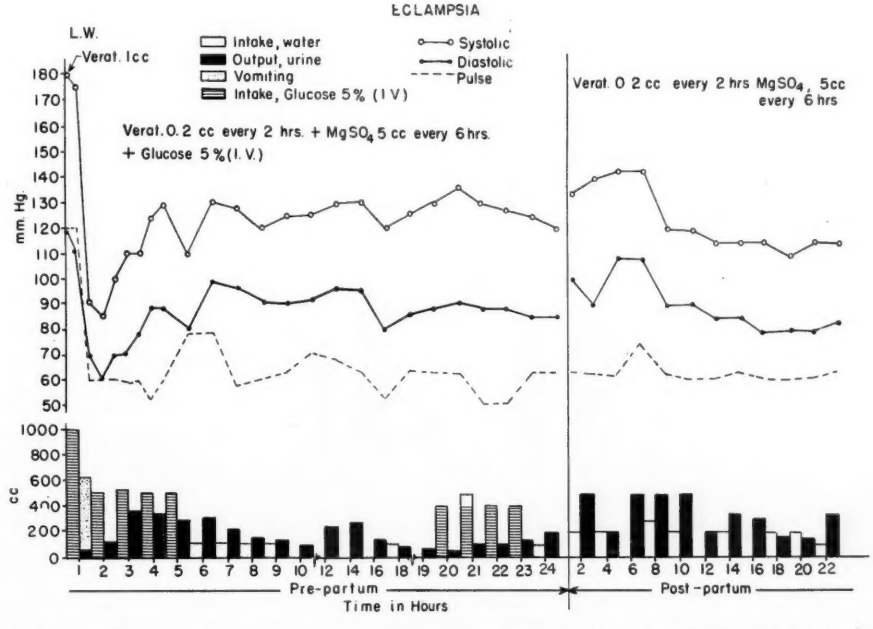

Fig. 8.—Pre- and postpartum study of an eclamptic patient who had no control period because of her poor condition.

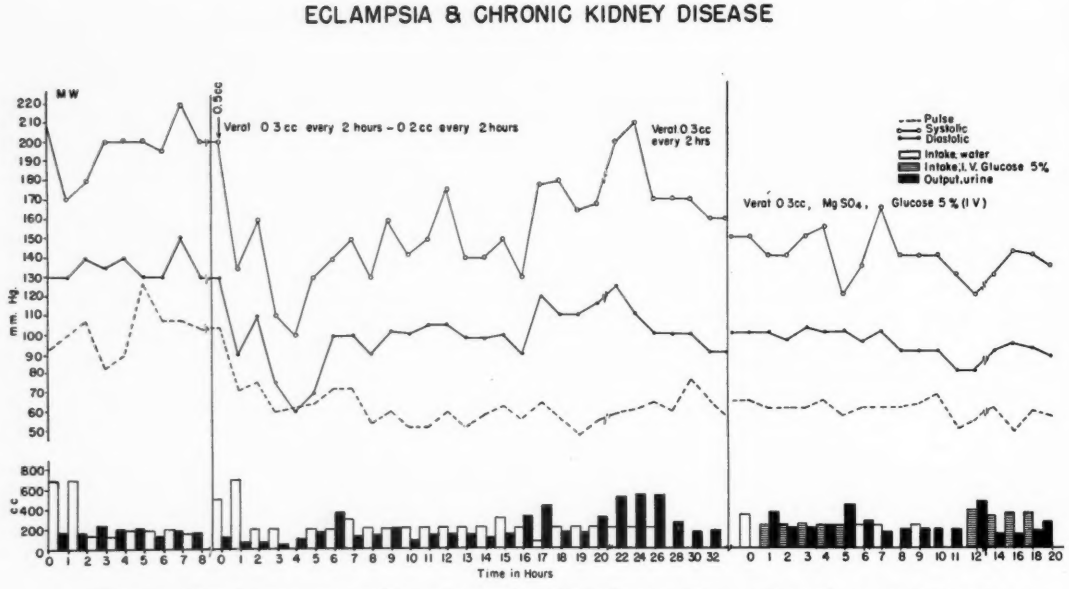

Fig. 9.—Blood pressure, pulse rate, and fluid balance of an eclampsia superimposed on chronic renal insufficiency. This patient left the hospital with blood urea nitrogen 60 and urine specific gravity 1.008.

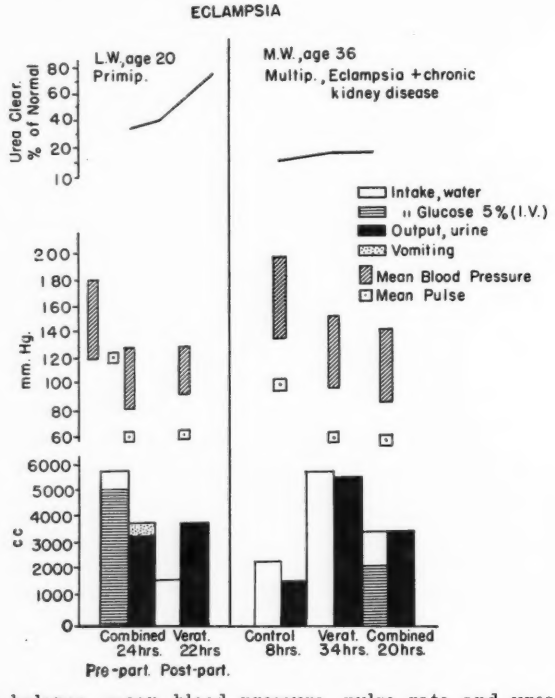

Fig. 10.—Total fluid balance, mean blood pressure, pulse rate and urea clearance variations of the two eclamptic patients.

In general, the patients with essential hypertension appeared to be more resistant to the action of veratrum viride, requiring larger doses to produce a satisfactory blood pressure fall.

C. *Eclampsia.*—Two patients with convulsive eclampsia were studied. The first (Fig. 8) was not studied in a control period due to the seriousness of her condition at the time of admission. She had had four convulsions at home and one upon arrival in the hospital. She was given 1 c.c. of veratrum viride within the first fifteen minutes and was continued then on the combined treatment before and after delivery.

1. *Urinary output:* The patient was catheterized at the time of admission, before the treatment was started, and no urine was obtained. After the next hour, the urinary output increased gradually and was maintained at an adequate volume, despite the marked fall in blood pressure and pulse rate. This patient showed profuse diuresis during the postpartum period.

2. *Urea clearance:* This test increased from 36.1 per cent to 42.2 per cent of normal while this patient was on the combined regimen before delivery, and to 76 per cent during the postpartum period.

The other eclamptic patient, who later proved to have chronic renal insufficiency, was studied for eight hours in the control period, thirty-six hours in the veratrum viride period and twenty-four hours in the combined period. Fig. 9 shows the urinary output and blood pressure variation in this patient. Fig. 10 illustrates the summary of both cases.

Discussion

Little, as yet, is known about the pharmacological action of veratrum viride. Several investigators[13, 14] have made an extensive study of some of the veratrum alkaloids in animals and have concluded that they have a definite vasodepressor and cardiodecelerator effect acting partially through a vagal reflex. In their studies, there was no mention about the effect of these alkaloids on renal blood flow or urine volume. Willson and Smith,[15] however, by the use of intravenous injections of veratrum viride in vagotomized animals observed an increase in the perfusion rate of kidneys and other isolated organs. They maintained that this drug has a definite peripheral vasodilating action independent of the vagus nerve. It decreases the blood pressure and increases the vascular bed of isolated organs without demonstrable change in the cardiac output.

This peripheral vasodilatation, together with the increased blood flow, has served as the theoretical basis for the clinical use of veratrum viride in the toxemias of pregnancy.[1-3] However, when the drug was given to pre-eclamptic and hypertensive pregnant patients, Willson[7, 8] observed a simultaneous decrease in the urinary output which reached dangerous levels. This finding was explained on the basis of a sudden decrease in the blood pressure and blood volume, and increase in the circulation time.

Freis et al.[16] using the catheterization method (Fick), found no alteration in either cardiac output or renal blood flow in hypertensive nonpregnant patients treated with veratrum viride although they observed a transitory oliguria following the first few doses.

The analysis of our results revealed the presence of a definite but transitory decrease in the urinary output following the first dose of veratrum viride. In no instance, however, did this decrease reach dangerous levels of oliguria or anuria. Harmful effects or symptoms of shock were not observed in any patient, despite the marked fall in blood pressure and pulse rate. A compensatory polyuria occurred invariably despite the continuation of the treatment. Some

pre-eclamptic patients (Fig. 11 as an example), because of delayed excretion of fluid intake, showed periods of transitory oliguria and compensatory polyuria even when they were not under any treatment. This might have led to incorrect conclusions had these patients not been observed for a long period of time.

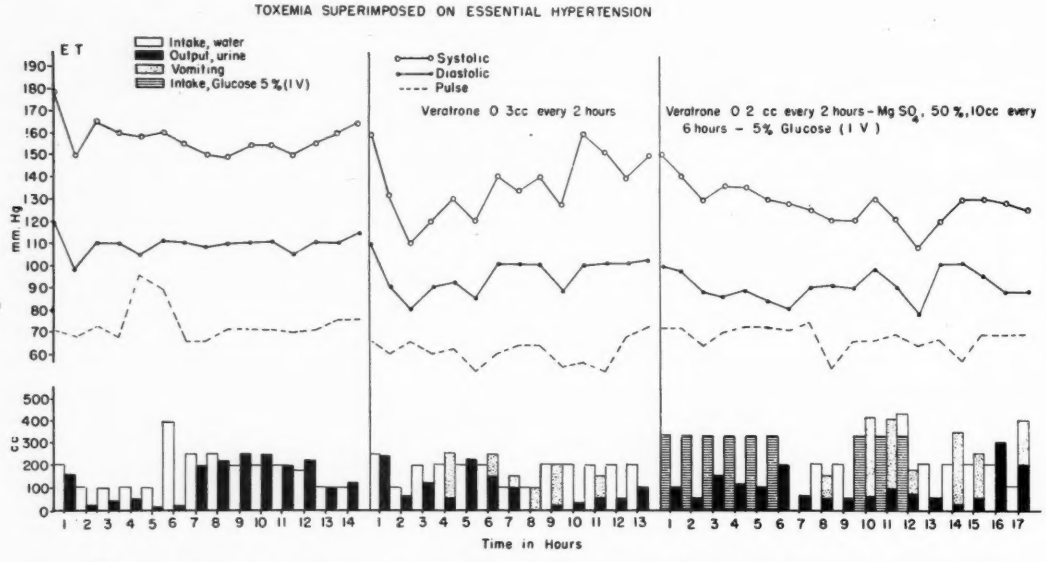

Fig. 11.—Severe pre-eclampsia with underlying essential hypertension. Note the two-hour oliguria in the control period. This patient tolerated veratrum viride poorly. Severe vomiting occurred even with small doses.

Further scrutiny of these data indicated that the decrease in urine volume was more marked when the following conditions existed:

a. A sudden fall in blood pressure and pulse rate consequent to the use of a large dose of the drug,

b. Severe vomiting and profuse diaphoresis leading to a loss of a large quantity of fluid by routes other than the kidneys,

c. When the fluid intake (already impaired by the nausea, vomiting, and diaphoresis peculiar to the action of veratrum viride) was insufficient to replace the fluid loss.

That a correlation between the sudden drop in blood pressure and the decrease in urine volume exists was evidenced by the fact that when veratrum viride was employed in proper dosage, not allowing the former to fall below 120 to 140 systolic and 80 to 90 diastolic, adequate diuresis was obtained. It could also be corroborated by the fact that, in the cases of normal pregnancy, where no decrease in blood pressure was noted with veratrum viride, the urine volume, similarly, showed no change.

Nausea, vomiting, and diaphoresis were considered important factors in decreasing the urinary output. The figures indicate that the lowest urine volumes were coincident with severe vomiting. With the use of proper dosage of veratrum viride these disturbing elements were minimal and the patients increased their oral fluid intake and consequently their urinary output.

Finally, the importance of an adequate fluide balance is evidenced by the fact that when the patients were given more fluid or when 5 per cent glucose in water, intravenously, was added to the treatment, the diuresis increased markedly. This low concentration of glucose has replaced entirely the hypertonic solution formerly used in this department, following the study of Peterson, Goodwin and Finland,[17] Maddock,[18] and Winslow.[19] It has proved to be a potent adjunct in promoting diuresis.

The addition of magnesium sulfate to the veratrum viride seemed to be of real value. Less veratrum viride was required to obtain the same blood pressure fall when both drugs were administered simultaneously. Consequently, there was less nausea and vomiting and the urinary output increased despite the fact that the blood pressure and pulse rate were maintained at lower levels.

The urea clearance test was of no help in detecting any impairment of kidney function as the result of the treatment with veratrum viride because the variations were similar to those encountered in normal individuals.

Although this series of cases is small, the uniformity of results permits us to conclude that the slight and transitory decrease in urine volume following the use of veratrum viride does not endanger the life of the patient in any way. It can possibly be explained by a relative and transitory hemostasis due to a sudden fall in blood pressure aggravated by the vomiting and profuse diaphoresis.

Summary

1. Eight pre-eclamptic, two eclamptic, three hypertensive and four normal pregnant patients were studied in control, veratrum viride, and combined periods.

2. The following changes were observed:

a. Normal pregnant patients showed no alteration in urine volume or blood pressure following the administration of veratrum viride.

b. Pre-eclamptic and hypertensive patients showed a slight decrease in the hourly urine volume following large doses of veratrum viride. A compensatory polyuria occurred thereafter, maintaining the total output for both periods in the same proportion.

c. No decrease in the urine volume was observed in the combined period.

3. The urea clearance test showed oscillations which were considered within the range of normal variability of the test.

4. A possible correlation between the variation in urine volume and the fall in blood pressure and pulse rate is discussed.

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Addendum

After this report had been submitted for publication, three additional cases of antepartum convulsive eclampsia were studied. All were comatose at the time of admission. Veratrum viride was administered intravenously in doses varying from 0.2 to 0.3 c.c. every hour. Fluid intake consisted chiefly of intravenous 5 per cent glucose in water.

Unfortunately, in all three cases, control periods were not obtained because of the serious condition of the patients and the necessity for immediate treatment. The following table outlines the data on these three patients:

NAME OF PATIENT TIME OBSERVED	MEAN B/P BEFORE TREATMENT	MEAN B/P AFTER TREATMENT	FLUID INTAKE (C.C.)	URINARY OUTPUT (C.C.)
M. F. 48 hours	210/120	130/82	5,100	3,300
G. R. 36 hours	180/110	120/60	4,200	2,950
L. U. 12 hours	220/102	130/70	3,000	2,700

The intravenous use of veratrum viride is now being extensively studied in this department and will form the subject of a future report.

PENICILLIN THERAPY IN THE OBSTETRICAL PATIENT

A Study of Its Effect on the Bacterial Flora of the Postpartum Uterus

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THE purpose of this paper is to present the results of an investigation of the effect of penicillin on the bacterial flora of the postpartum uterus. Harris and Brown[1] showed that the gravid uterus is ordinarily sterile before the 6th hour of labor but is usually not sterile after that time; and various other investigators have established the fact that the postpartum uterus almost always contains numerous bacteria.[2, 3] This study was undertaken in order to determine what effect, if any, penicillin administration may have on such bacteria; how morbidity and complications may be affected; and what would be the possibility of complete sterilization of the uterine cavity by this means in the first few days post partum.

Methods

Cultures were obtained from the uterine cavities of 86 postpartum patients, 54 of whom received varying amounts of penicillin and 32 of whom were untreated. The material was obtained by a new technique which has been described elsewhere,[4] and which, we believe, greatly reduces contamination by organisms from the vagina and cervix. This was substantiated by the fact that a number of uterine cultures, not included in our series, which were taken with a Little tube[5] from patients receiving intramuscular penicillin, all showed bacterial contaminants; while, in a similar group of patients on the same therapy, culture material taken by the new technique was often sterile (Table III). Therefore, we think that the organisms isolated in the control series of untreated patients represents the true bacterial flora of the postpartum uterus, and that the results of the cultures taken from patients receiving penicillin represent a true picture of the effect of penicillin on such organisms in the postpartum uterus.

The material collected from the uterine cavity was immediately inoculated into Brewer's thioglycollate medium[6] and sent to the laboratory. Here 0.1 c.c. of a 4 per cent sterile solution of clarase (final concentration 0.25 per cent) was added to the culture to neutralize any penicillin which might be present in the inoculum, and 2 c.c. of sterile ascitic fluid (final concentration 20 per cent) to enhance the growth of pleuropneumonia-like organisms. Methods followed for the isolation and identification of the various bacteria were those outlined in Schaub and Foley's "Diagnostic Bacteriology," third edition.[7] The penicillin sensitivity of all organisms isolated was determined by the paper disc technique described by Bondi and associates,[8] and the results are given in Table II.

The organisms isolated from the uterine cultures were of the species generally accepted as representing the normal flora of the postpartum uterus with but one exception. A review of the literature has shown that this is the first

report of the isolation of pleuropneumonia-like organisms from material from the uterine cavity. Methods used for the isolation and identification of these organisms will be reported elsewhere.[9] Their significance in the postpartum uterus is not definitely known, but the clinical course of the patients from whom they were isolated suggests that, at least in these cases, they were nonpathogenic. The role of pleuropneumonia-like organisms in genitourinary diseases has recently been reviewed by Dienes and associates.[10] They report their occurrence in 26 per cent of cervical and vaginal cultures, and conclude "the relatively high incidence of this organism in the female genital tract suggests that it is part of the normal bacterial flora in this location." Similar findings have been reported by other investigators.[11, 12, 13] In view of the frequent occurrence of pleuropneumonia-like organisms in the normal vagina and cervix, the isolation of these organisms from the postpartum uterus is not surprising.

Presentation of Material

As a control series, cultures were obtained from 32 postpartum patients who received no antibiotic. Of these, 27 had spontaneous deliveries and 5 were delivered by low forceps and had episiotomies (Table 7). These cases were not studied consecutively, but the cultures were obtained in the same period as those in the penicillin-treated series. That is, each time a group of patients on penicillin were cultured, a control culture was taken on an untreated patient.

Patients in the control series were selected on the basis of a normal temperature up until the time the culture was taken, since we purposely limited the investigation to the study of the bacterial flora of the normal postpartum uterus and the effect of penicillin on such flora. Cultures in the control series were obtained 36 to 72 hours after delivery.

The findings in this control group are shown in Table I. With the exception of two cases in which the cultures were sterile, the remaining 30 cases showed various bacteria, predominantly anaerobic streptococci (81.3 per cent) and *Bacteroides* (50 per cent), Table III. The penicillin sensitivity of these organisms was determined and results recorded in Table II. This reveals that the predominating organisms, anaerobic streptococcic and *Bacteroides,* are highly sensitive to penicillin, while the organisms occurring less commonly are either resistant or moderately sensitive.

TABLE I. BACTERIA ISOLATED FROM UTERINE CULTURES OF CONTROL SERIES OF 32 PATIENTS WHO RECEIVED NO PENICILLIN, AND REPRESENTING THE NORMAL FLORA OF THE POSTPARTUM UTERUS

BACTERIA	NO. OF CASES	NO. OF STRAINS ISOLATED
Anaerobic gamma streptococci	23	36
Anaerobic beta streptococci	7	7
Microaerophilic gamma streptococci	2	3
Microaerophilic beta streptococci	2	2
Aerobic alpha streptococci	2	2
Aerobic gamma streptococci	1	1
Streptococcus fecalis	1	1
Staphylococcus albus	2	2
Gaffkya anaerobia	3	3
Bacteroides	16	19
Escherichia coli	2	2
Aerobacter aerogenes	1	1
Aerobic diphtheroides	1	1
Anaerobic diphtheroides	2	2
Lactobacilli	1	1
Pleuropneumonia-like organisms	1	1
Sterile	2	

TABLE II. PENICILLIN SENSITIVITY* OF BACTERIA ISOLATED FROM UTERINE CULTURES

HIGHLY SENSITIVE TO PENICILLIN†	MODERATELY SENSITIVE TO PENICILLIN‡	RESISTANT TO PENICILLIN§
Anaerobic gamma streptococci	*Staphylococcus albus*	*Streptococcus fecalis*
Anaerobic beta streptococci	Aerobic diphtheroides	*Escherichia coli*
Microaerophilic gamma streptococci	Anaerobic diphtheroides	*Aerobacter aerogenes*
Microaerophilic beta streptococci		Pleuropneumonia-like organisms
Aerobic alpha streptococci		
Aerobic gamma streptococci		
Gaffkya anaerobia		
Bacteroides		

*Determined by the paper disc method of Bondi, A., Spaulding, E. H., Smith, D. E., and Dietz, C. D., Am. J. M. Sc. 213: 221-225, 1947.

†20 to 40 mm. zone of penicillin inhibition; sensitive to less than 0.1 unit per ml.

‡10 to 20 mm. zone of penicillin inhibition; sensitive to 0.1 to 0.4 units per ml.

§No zone of inhibition around penicillin disc.

TABLE III. SUMMARY OF THE INCIDENCE OF PREDOMINATING ORGANISMS IN THE POSTPARTUM UTERUS ON PATIENTS WITH AND WITHOUT PENICILLIN

	UNTREATED PATIENTS IN CONTROL SERIES		PENICILLIN-TREATED SERIES	
	CASES	PER CENT	CASES	PER CENT
Total cases	32	100.0	54	100.0
Sterile cultures aerobically and anaerobically (absolutely*)	2	6.2	32	59.4
Anaerobic streptococci of some type found	26	81.3	8	14.8
Bacteroides (anaerobic gram-negative bacilli)	16	50.0	2	3.7

*If cultures showing pleuropneumonia-like organisms are considered as equivalent to being sterile, the percentage of sterile cultures in the control series remains *6.2 per cent*, while the percentage of sterile cultures in the penicillin series becomes *74.1 per cent*.

Uterine cultures were obtained from 54 patients who received penicillin therapy. The patients in this series were selected by chance, since the patients were placed on penicillin as soon as they reached the delivery floor. One-half of the series consisted of Negro women, the other of white women. Of the 54 cases, 34 delivered spontaneously (Table VII). There were thirteen patients who were delivered by elective low forceps and five by indicated low forceps, for such reasons as prolonged second stage, breech deliveries, toxemia, twins, and contracted outlets. Two patients were delivered by low cervical cesarean section. Eighteen episiotomies were performed in all. In this series, there were two cases of prolonged ruptured membranes over 24 hours, two of prolonged second stage, five cases of second degree tear, one of third degree tear, one operative induction of labor, one postpartum Pomeroy tubal ligation and one case of uterine inertia.

The amount of penicillin given the patients in this series was intentionally varied, in order to determine the smallest dosage effective in sterilizing the uterine cavity. As shown in Table IV, the largest amount was 400,000 units daily of aqueous penicillin given intramuscularly in divided doses of 50,000 units every three hours until the time the culture was taken. The smallest amount was a single intramuscular injection of 200,000 units of penicillin which the patient received on being admitted to the delivery floor. There were six miscellaneous cases which received varying dosages which did not fit into the regular groups, as shown in Table IV.

The period elapsing between the time of delivery and the time the cultures were taken was also deliberately varied, in order to determine how long the uterine cavity would remain sterile. The majority of cultures were taken between 36 and 72 hours after delivery, as shown in Table V.

TABLE IV. BACTERIA ISOLATED FROM UTERINE CULTURES OF 54 PATIENTS RECEIVING PENICILLIN

NO. OF CASES	PENICILLIN DOSAGE (UNITS)	STERILE	PLEURO PNEUMONIA-LIKE	ANAEROBIC BETA STREP.	ANAEROBIC GAMMA STREP.	BACTEROIDES	E. COLI	AEROBACTER AEROGENES	GAFFKYA	DIPHTHEROIDES ANAEROBIC AND AEROBIC	TOTAL CASES SHOWING ALL ORGANISMS	CASES ☿ BACTERIA EXCLUSIVE OF PLEUROPNEUMONIA-LIKE ORGANISMS
6	50,000 q. 3. h.	4	2					1			2	1
6	100,000 q. 8. h.	5		1							1	1
4	100,000 q. 12. h.	2	1				1				2	1
9	200,000 q. 24. h.	5	2				1			1	4	1
9	200,000 Stat. on Admis. 200,000 1 hr. PP	6	3	1	1				1	1	3	2
14	200,000 Stat. on Admis.	6	3	3	5	2	1			1	7	7
Miscellaneous dosages												
6	*	4	1					1			2	1
Totals												
54		32 or †59.4	12 or 22.3	5 or 9.27	6 or 11.1	2 or 3.71	3 or 5.5	2 or 3.71	1 or 1.85	3 or 5.5	21 or 38.88	14 or 25.92

*3 patients were on 50,000 units every 3 hours, stopped at delivery.

3 patients received penicillin in oil and wax, one of whom received 300,000 units every 24 hours pre-delivery only; one of whom received 300,000 units every 24 hours; one of whom received a single dose of 300,000 units on first postpartum day.

†74.07 per cent of these cases were sterile, or sterile and contained pleuropneumonia-like organisms.

TABLE V. RESULTS OF UTERINE CULTURES ON PATIENTS RECEIVING PENICILLIN CORRELATED WITH THE TIME FROM THE HOUR OF DELIVERY TO TIME THE CULTURE WAS TAKEN

HOURS FROM TIME OF DELIVERY TO TIME OF CULTURE	NUMBER OF CASES	CASES ABSOLUTELY STERILE	CASES WITH PLEUROPNEUMONIA-LIKE ORGANISMS ONLY	CASES SHOWING OTHER ORGANISMS
0 to 24 hours	1	1	–	–
24 to 36 hours	4	3	–	1 Diphtheroids only
36 to 48 hours	17	13	3	1 Anaerobic Beta Strep. Light growth after 48 hours
48 to 72 hours	23	11	4	8
72 hrs. or more	9	4	1	4
Total cases	54	32	8	14

Total cases with pathogens	14	
Total cases without pathogens	40	
Percentage of sterile cases with or without pleuropneumonia-like organisms		74.07 per cent

The bacteriological findings in the uterine cultures from the 54 patients receiving penicillin are shown in Table IV. Of these, 32 (59.4 per cent) were sterile aerobically and anaerobically regardless of the penicillin dosage or time of culture. In addition, 8 cases (14.8 per cent) showed only pleuropneumonia-like organisms, which are penicillin resistant and, as previously noted, probably nonpathogenic. If pleuropneumonia-like organisms be regarded as clinically insignificant, then 40 cases or 74.1 per cent of the series were free of clinically significant organisms. From a total of 22 cases various organisms were isolated, as shown in Table V, but only 14 (25.9 per cent) revealed bacteria other than those of the pleuropneumonia group. Of these, 8 cases showed anaerobic streptococci, in which anaerobic beta streptococci occurred 5 times and anaerobic gamma streptococci 6 times. As to the few other organisms isolated from patients receiving penicillin, the Gram-negative bacilli, *Escherichia coli* and *Aerobacter aerogenes,* were found to be penicillin resistant, while *Gaffkya* and the aerobic and anaerobic diphtheroids were only moderately sensitive to penicillin, and the latter are of questionable pathogenicity.

Comparison of results obtained in the two series is best demonstrated in Table III. This table shows that 6.2 per cent of the cultures in the control series were sterile, whereas 59.4 per cent of the penicillin series showed no growth aerobically or anaerobically. The predominating organisms isolated from the control cultures were anaerobic streptococci (81.3 per cent) and *Bacteroides* (50 per cent), while in the penicillin series the incidence of these organisms was 14.8 per cent and 3.7 per cent, respectively.

In Table V is presented a correlation of the cultural results and the time at which the culture was taken. Here it is shown that, as the time after delivery is lengthened, the incidence of bacterial invasion of the uterus is increased. In Table VI the 14 cases in the penicillin series which showed bacteria other than pleuropneumonia-like organisms are classified according to the amount of penicillin received and the time at which the culture was taken. This table reveals that the majority of positive cultures were obtained from those cases receiving only a single injection of 200,000 units of aqueous penicillin intramuscularly on admission to the delivery floor, and further shows that the majority of positive cultures were obtained later than 48 hours following delivery.

We believe that these 14 cases should be analyzed at this time.

In the cultures taken 24 to 36 hours after delivery, one (No. 91) contained anaerobic diphtheroids, probably nonpathogenic and only moderately sensitive to penicillin. This patient had received 200,000 units of penicillin intramuscularly, in one injection every 24 hours. She was a 15-year-old Negro girl with one living child, who delivered spontaneously, and whose only complicating factor was a first degree vaginal tear and a second degree perineal tear. In the 36 to 48 hour period, one case (No. 70) showed a late growth of anaerobic streptococci. This patient had received 100,000 units of penicillin intramuscularly every 8 hours. She was a 21-year-old Negro woman with three living children, who delivered spontaneously without unusual incident. In the 48 to 72 hour period there were 8 cases which showed organisms. Five of these received only a single injection of 200,000 units of penicillin on admission, and from all of these 5 cases anaerobic streptococci were cultured, as well as *Bacteroides* from 2 cases and diphtheroides and pleuropneumonia-like organisms from another case. All 5 of these patients delivered spontaneously without untoward incident, with the exception of one whose only complication was a second degree tear. Of the other three cases in the 48 to 72 hour group, two of these patients received 50,000 units of penicillin every 3 hours, and from these penicillin-resistant *Aerobacter aerogenes* was cultured. One of these patients was a 22-year-old Negro woman with two living children, who delivered spontaneously without untoward incident, while the other was a 34-year-old Negro woman with two living children, who delivered spontaneously after

TABLE VI. PENICILLIN SERIES: TABLE CORRELATES DOSAGE AND TIME CULTURE WAS TAKEN IN THOSE CASES SHOWING BACTERIA, EXCLUSIVE OF PLEUROPNEUMONIA-LIKE ORGANISMS

PENICILLIN DOSAGE	50,000 U. Q.3.H.	100,000 U. Q.8.H.	100,000 U. Q.12.H.	200,000 U. Q.24.H.	200,000 U. STAT. ON ADMISSION AND 200,000 U. ONE HOUR POSTPARTUM	200,000 U. STAT. ON ADMISSION
0-24 hrs.						
24-36 hrs.				1 Case No. 91 had diphtheroids		
36-48 hrs.		1 Case No. 70 Light growth anaerobic beta strep.				
48-72 hrs.	2 Cases No. 67 Aerobacter No. 44 Aerobacter		1 Case No. 73 *E. coli*			5 Cases *No.* 27 Anaerobic gamma strep. 30 Micro. gamma strep. 97 Micro. beta strep. Anaero. gamma strep. Micro. diphtheroids Pleuropneumonia-like 108 Anaero. gamma strep. and *Bacteroides* 107 Anaero. beta strep. *Bacteroides*
72 hours					2 Cases No. 103 *Gaffkya*, Anaero. diphtheroids No. 109 Anaero. gamma strep. 3 strains Anaero. beta strep. Pleuropneumonia	2 Cases No. 105 Anaero. gamma strep. Anaero. beta strep. No. 95 *E. coli*

TABLE VII. TABLE OF CLINICAL MATERIAL SHOWING DISTRIBUTION OF PATIENTS AND OBSTETRICAL FACTORS

Penicillin Series

RACE	NUMBER OF CASES	SPONTANEOUS DELIVERIES	ELECTIVE LOW FORCEPS	OPERATIVE DELIVERIES	EPISIOTOMIES	COMPLICATIONS	TEMPERATURE	
							NORMAL	MORBIDITY*
White	27	17	7	3 a. Prolonged second stage b. Breech delivery c. Contracted outlet	10	2 Prolonged ruptured membranes 1 Prolonged second stage 3 Second degree tears 1 Third degree tear	27	–
Negro	27	17	6	4 a. Twins b. 1 Toxemia c. 2 Low cervical sections	8	1 Prolonged second stage 2 Second degree tears 1 Operative induction of labor 1 Tubal ligation 1 Uterine inertia	26	1†
Total	54	34	13	7	18	12	53	1

*Morbidity; Any case with a temperature of 100.4° F. on any two consecutive days.

†Case 25 had uterine inertia for three days and prolonged ruptured membranes. Received penicillin 50,000 U. q.3.h. preoperatively. Had a low cervical section. Then penicillin in oil and wax 300,000 U. q.24.h. Temperature normal first day; second day 102° F.; third day 100° F.; fourth day 100° F.; then normal. Uterine culture sterile on third postpartum day. Etiology of temperature unknown, or operative reaction.

*Series Without Penicillin**

RACE	NUMBER OF CASES	SPONTANEOUS DELIVERIES	ELECTIVE LOW FORCEPS	OPERATIVE DELIVERIES	EPISIOTOMIES	COMPLICATIONS	TEMPERATURE	
							NORMAL	MORBIDITY
White	4	3	1	–	1	1 Second degree tear	4	–
Negro	28	24	2	2 a. Indicated low forceps, toxemia b. Indicated low forceps, prolonged second stage	4	1 Second degree tear 1 Upper respiratory infection 1 Infected episiotomy 1 Prolonged second stage	27	1†
Total	32	27	3	2	5	5	31	1

*Control series were taken from patients who had no temperature elevations in order that any possible infections would be excluded.

†Case No. 47. Temperature rise etiology unknown.

having four vaginal examinations and whose labor was operatively induced. The third patient had received 100,000 units of penicillin every 12 hours, and the culture yielded penicillin-resistant *Escherichia coli.* She was a 21-year-old white woman with no living children, whose only complication was a third degree perineal laceration.

Four of the 14 positive cultures were taken over 72 hours after delivery. Two of these patients received a single injection of 200,000 units of penicillin on admission and the same amount one hour post partum. These cases yielded *Gaffkya,* anaerobic diphtheroides, anaerobic streptococci and pleuropneumonia-like organisms. The other two patients received only a single injection of 200,000 units of penicillin on admission and showed anaerobic streptococci from one case and *E. coli* from the other. All of these patients delivered without untoward incident. Case No. 95, which yielded *E. coli,* was a patient who had a Pomeroy sterilization post partum for grand multiparity

As shown in Table VII, there was only one case in the penicillin series that had a temperature elevation of 100.4° F. or more on any two days post partum. This patient had uterine inertia for three days and prolonged ruptured membranes. She was placed on penicillin, 50,000 units every 3 hours, 24 hours after the membranes ruptured, and therapy was continued until the time of operation. She was delivered by a low cervical cesarean section and was placed on penicillin in oil and wax, 300,000 units daily. Her temperature on the second postoperative day was 102° F., the third day 100.4° F., the fourth day 100° F., and thereafter her temperature was normal. The uterine culture taken on the third postoperative day was sterile. No cause for the temperature elevation could be found.

The morbidity in the two series of patients is not comparable, since the patients in the control series were selected on the basis of a normal temperature, as mentioned before, whereas patients in the penicillin series were selected at random when they reached the delivery floor, and were followed regardless of their complications. However, it seems to us that the low morbidity in the penicillin series may be significant, although the series is obviously too small to be conclusive.

Discussion

Even though this study is open to criticism because of the limited number of cases involved, we think that we are justified in reporting the results at this time because they seem sufficiently convincing. The incidence of sterile cultures in the penicillin series as contrasted with the control series, 59.4 per cent as against 6.2 per cent, is certainly significant. If we may discount the presence of the penicillin-resistant, probably nonpathogenic pleuropneumonia-like organisms, then the number of cultures showing no significant organisms in the penicillin-treated cases is 74.1 per cent. As shown in Tables I and II, the predominating organisms in the control series were penicillin-sensitive anaerobic streptococci and *Bacteroides,* both of which were markedly decreased in the penicillin series (Table III). As shown in Table IV, from only one patient receiving larger doses of penicillin was a penicillin-sensitive anaerobic streptococcus isolated, the only other organisms occurring in such cases being penicillin-resistant *A. aerogenes* and *E. coli,* and a probably nonpathogenic diphtheroid. All but one of the cases in the penicillin series which showed penicillin-sensitive *Bacteroides* and anaerobic streptococci were those on low penicillin dosages and those in which cultures were taken later than 48 hours after delivery. This would seem to indicate that relatively high dosages of penicillin, given prepartum and postpartum, may eliminate penicillin-sensitive organisms from the uterus for at least three days or more post partum, and that a small amount given early in labor may be effective up to 48 hours following delivery.

The fact that penicillin therapy will usually disinfect the postpartum uterus, as suggested in this study, has the possibility of wide practical use. Further investigations on a large scale, however, will be necessary in order to confirm the clinical applications here suggested.

Summary

1. Uterine cultures were taken from 86 postpartum patients, 54 of whom received varying amounts of penicillin, and 32 of whom received no antibiotic therapy.

2. From 30 of the 32 cultures in the control series from untreated patients, various bacteria were isolated, predominantly anaerobic streptococci and *Bacteroides*.

3. Of the uteri of 54 patients receiving penicillin therapy, 32 were sterile, aerobically and anaerobically, and eight yielded only pleuropneumonia-like organisms.

4. Only fourteen cultures in the penicillin series showed significant bacteria, four of which were penicillin-resistant coliform organisms. All but one of the penicillin-sensitive organisms occurred in cultures taken more than 48 hours after delivery, from patients receiving small amounts of penicillin.

5. The possibility of disinfecting the postpartum uterus by penicillin therapy has obvious clinical applications.

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EFFECT OF BIRTH ON MENTALITY

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THE purpose of this paper is to show the effect of pregnancy and labor on the intelligence quotient and personality of the infant.

Method

The 453 cases studied are the children attending the Rocky Mount High School, provided they were born in the city. Also included are the last two years' graduates and the children who withdrew from the high school in the past few years. The earliest birth was in 1926 and the latest in 1933.

All of the fifteen doctors who delivered these patients were general practitioners, but one had two years' residency at the New York Lying-In Hospital. The cesarean sections were done by two surgeons, both Fellows of the American College of Surgeons, and one a member of the American Board of Surgery. One delivery was attended by a midwife.

One hundred forty births were in hospitals; the remaining 313 were home deliveries. No records could be found in the doctors' offices of these 313, other than the names of the mothers and the dates of the deliveries. Six of the doctors were dead, one had moved away, and the remaining eight had moved their offices, or stopped doing obstetrics, and the records were lost. Questionnaires were therefore sent to the mothers.

The accuracy of the answers was better than had been expected. Sixty-nine of the hospital-delivered mothers returned questionnaires showing 89.1 per cent accuracy in reporting spontaneous deliveries, and 92.3 per cent in reporting forceps. The greatest inaccuracy was in reporting breech deliveries. Of 41 reported breeches, only 13 were finally considered so after telephone conversations with the mothers or second questionnaires where no telephone was available. Three of the 13 were not reached but were left in the group listed as breech. This left 2.87 per cent breech deliveries, comparable with the usually reported 3 per cent. The mothers' listing of parity was not questioned. The estimates of weight gain and hours of labor are highly questionable, but no method of checking this could be found, since these were not mentioned on the hospital records. The weights of babies are probably fairly accurate as the home-delivered babies were weighed by the attending doctors. The mothers' ages were taken from hospital records or birth certificates.

The IQ rating was the highest recorded of the 1 to 4 listed on the high school records; this was considered more truly representative of the child's ability. The mental tests were mostly Pintner Cunningham, Pintner Intermediate, and National Intelligence Test. A few were the California Mental Maturity Test and the Stanford-Binet in addition to the above. The personality rating is an average of individual ratings in cooperation, courtesy, dependability, industriousness, initiative, leadership, maturity, self-control, and personal appearance. A personality rating of 1 is superior, 2 above average, 3 average, 4 below average, and 5 low.

Results

From Table I, it is seen that the total group of 453 cases had an average IQ of 110.04 and personality rating of 2.27. In all groups except cesarean section, the children of primiparous mothers had a slightly higher IQ than those born of multiparas. Forceps and spontaneous deliveries resulted in a slightly lower IQ than breech, cesarean sections, and versions. (The small number of the three latter is probably misleading.) Of seven cesareans, only 2 patients were nontoxic, and the children of these two average the highest IQ in the entire series (126). All seven cesarean-born children have an average IQ of 114, which is higher than that following any other type of delivery. The personality ratings show the most favorable figures for cesarean sections, then spontaneous delivery, then breech, then version, and, last, forceps deliveries.

TABLE I

	PERSONALITY RATING	IQ		PERSONALITY RATING	IQ		PERSONALITY RATING	IQ
Total Group, 453 Cases			*147 Primiparas*			*294 Multiparas*		
	2.27	110.04		2.55	112.53		2.11	108.9
Male	2.26	108.2	Male	2.64	112.11	Male	1.91	106.26
Female	2.28	112.12	Female	2.15	112.70	Female	2.33	111.90
380 Spontaneous Deliveries			*107 Primiparas*			*265 Multiparas*		
	2.11	109.9		2.35	112.05		2.08	109.05
Male	2.05	108.21	Male	2.62	112.45	Male	1.74	106.55
Female	2.28	111.63	Female	2.11	111.67	Female	2.34	111.71
49 Forceps Deliveries			*31 Primiparas*			*14 Multiparas*		
	3.06	109.51		3.3	112.17		2.57	103.77
Male	3.32	107.91	Male	3.63	111.19	Male	2.68	101.5
Female	2.43	113.3	Female	2.44	114.47	Female	2.31	111.33
13 Breech Deliveries			*4 Primiparas*			*9 Multiparas*		
	2.45	112.85		2.75	124.25		2.32	107.11
Male	2.37	108.86	Male	3.7	136.	Male	2.15	104.33
Female	2.54	116.5	Female	2.43	120.3	Female	2.64	112.67
7 Cesarean Births			*3 Primiparas*			*4 Multiparas*		
	1.93	114.		2.13	104.		1.78	121.5
Male	2.23	110.7	Male	2.2	101.5	Male	2.3	129.
Female	1.7	116.5	Female	2.	109.	Female	1.6	119.
2 cases (nontoxic cesareans)	1.9	126.						
4 Versions			*2 Primiparas*			*2 Multiparas*		
	2.55	114		1.85	121.5		3.25	106.5
			Both female			Both male		

Personality rating: 1, superior; 2, above average; 3, average.

Note: In a few instances, parity was unknown; occasionally, sex also was not established from the records; these appear in the totals in the left-hand columns in these tables, but not in the subdivisions.)

Table II shows that eclamptic mothers have children with the lowest IQ in the entire series (101.2). This is more severe in primiparas than multiparas. Pre-eclampsia also results in a low IQ, but here multiparas are more affected than primiparas.

Only 13 children had jaundice as newborns; there is no drop in IQ, but the small number of cases may be misleading.

The effect of probable Pituitrin is striking. (The mothers were asked if they had received injections to hasten labor; the only other hypodermic injection these women were likely to have received in labor is morphine; hyoscine was not

used even in hospital deliveries at that time.) The drop is from 110.04 for the whole series to 105.11 in the probable Pituitrin group, and to 99.85 in the male multiparous births. Personality rates roughly follow the same pattern. The fast labors are a suspicious factor in lower IQ.

TABLE II. EFFECT OF TOXEMIA, JAUNDICE, AND PROBABLE PITUITRIN

	PERSONALITY RATING	IQ		PERSONALITY RATING	IQ		PERSONALITY RATING	IQ
Eclampsia 6 Cases			*5 Primiparas*			*1 Multipara*		
	2.75	101.2		2.78	95.75		2.6	126.0
4 males	2.95	104.	3 males	3.07	94.5	1 male	2.6	126.0
2 females	2.35	97.	2 females	2.35	97.			
41 Pre-eclampsia			*13 Primiparas*			*27 Multiparas*		
	2.57	105.89		2.71	110.5		2.44	102.85
24 males	2.86	104.46	Males	3.43	110.43	Males	2.67	102.
17 females	2.03	108.9	Females	2.1	110.53	Females	2.98	105.7
13 Jaundiced Babies			*6 Primiparas*			*7 Multiparas*		
	2.51	112.27		2.53	120.4		2.5	105.5
8 males	2.85	114.	5 males	2.74	118.75	3 males	3.03	104.5
5 females	1.98	110.4	1 female	1.5	128.	4 females	2.1	106.
62 Cases Probably Receiving Pituitrin			*20 Primiparas*			*42 Multiparas*		
	2.54	105.11		2.3	111.4		2.64	102.18
Males	2.68	101.86	Males	2.34	106.89	Males	2.8	99.85
Females	2.41	108.68	Females	2.26	117.22	Females	2.49	104.63
For Comparison: Entire Group (453)			*147 Primiparas*			*294 Multiparas*		
	2.27	110.04		2.55	112.53		2.11	108.9
Males	2.26	108.2	Males	2.64	112.11	Males	1.91	106.26
Females	2.28	112.12	Females	2.15	112.7	Females	2.33	111.90

In Table III, chloroform deliveries are associated with a higher IQ than deliveries under ether. Chloroform being administered with more oxygen results in less anoxemia to the infant; the difference is more probably explained by the fact that most of the chloroform anesthesias were light and short, while most of the hospital deliveries were under almost surgical depth ether anesthesia. The final total anesthesia includes known ether and chloroform and cases where anesthesia must have been used due to the type of delivery (version and forceps), but no mention of the type of anesthesia was found. Personality rates are comparable to the IQ in the anesthesia group.

TABLE III. ANESTHESIA

	PERSONALITY RATING	IQ		PERSONALITY RATING	IQ		PERSONALITY RATING	IQ
123 Chloroform			*39 Primiparas*			*84 Multiparas*		
	2.39	111.72		2.25	115.61		2.47	109.77
Male	2.57	110.59	Male	2.29	115.77	Male	2.77	107.6
Female	2.21	113.2	Female	2.14	116.56	Female	2.24	111.84
33 Ether			*18 Primiparas*			*15 Multiparas*		
	2.45	107.67		2.51	101.2		2.37	114.13
Male	2.8	103.78	Male	2.64	98.3	Male	3.	110.78
Female	2	113.5	Female	2.34	107.85	Female	1.66	119.17
179 Total Anesthesia			*72 Primiparas*			*107 Multiparas*		
	2.4	111.08		2.37	112.26		2.42	110.18
Male	2.62	108.91	Male	2.49	110.58	Male	2.71	107.59
Female	2.16	113.92	Female	2.2	115.7	Female	2.13	112.93

Personality rating: 1, superior; 2, above average; 3, average.

In Table IV, a marked drop in IQ is seen for labors over 30 hours and under one hour. For all labors of 25 hours or under, multiparas have children with a lower IQ than primiparas, suggesting that the faster the labor the lower the IQ. Personality ratings are best (lowest) in the 25- to 30-hour group, and least favorable in labors over 30 hours, and second worse in the labors under one hour.

TABLE IV. HOURS OF LABOR

	PERSONALITY RATING	IQ		PERSONALITY RATING	IQ		PERSONALITY RATING	IQ
One Hour or Less						*10 Multiparas*		
	2.68	105.8					2.68	105.8
						5 males		99.8
						5 females		111.8
Over 1, Through 3 Hours 77 Cases			*9 Primiparas*			*68 Multiparas*		
	2.36	109.86		2.1	114.22		2.39	109.25
Male		108.12	3 males		98.67	42 males		108.79
Female		112.66	6 females		122.	22 females		110.12
						Sex not mentioned in 4 cases		
Over 3, Through 6 Hours 93 Cases			*8 Primiparas*			*85 Multiparas*		
	2.35	111.16		2.6	117.17		2.32	110.69
Male		110.3	4 males		125.5	43 males		109.02
Female		112.	4 females		113.	42 females		112.31
Over 6, Through 15 Hours 102 Cases			*44 Primiparas*			*58 Multiparas*		
	2.55	110.37		2.6	112.14		2.5	109
Male		108.16	24 males		113.95	22 males		102.1
Female		112.	20 females		110.15	36 females		113.4
Over 15, Through 25 Hours 29 Cases			*19 Primiparas*			*10 Multiparas*		
	2.37	111.58		2.2	111.94		2.71	110.75
Male		111.93	9 males		117.89	5 males		101.2
Female		111.17	10 females		106	5 females		126.67
Over 25, Through 30 Hours 4 Cases			*3 Primiparas*			*1 Multipara*		
	2.05	110		2.2	109		1.6	112
Over 30 Hours 11 Cases			*4 Primiparas*			*7 Multiparas*		
	2.75	102		2.25	99.75		3.18	103.28
Male		98.85						
Female		111.33						

Personality rating: 1, superior; 2, above average; 3, average.

Table V classifies IQ according to infant birth weight. Birth weights of 5 pounds or under are probably the best index of prematurity. (Only eight of this group were reported as premature; seven more were reported premature in the 5- through 6-pound group; and 17 babies over 6 pounds were considered premature by their mothers.) The results are a little surprising as the babies weighing 5 pounds or under have a higher IQ than the average for the whole series (111.9), while those over 5 through 6 pounds show a marked drop in IQ (105.24); however, the ones considered premature by their mothers in this group average 115. A significant drop is again seen when birth weights are over 9 pounds (108.8). Personality rates are best (lowest) in the 5-pound or under group and become steadily worse as the birth weights increase.

TABLE V. WEIGHT OF BABY

	PERSONALITY RATING	IQ		PERSONALITY RATING	IQ		PERSONALITY RATING	IQ
5 Pounds or Under, 13 Cases			*4 Primiparas*			*9 Multiparas*		
	2.22	111.9		2.9	101.		2.12	116.78
4 males	2.33	116	2 males	2.45	108.5	2 males	2.2	123.5
9 females	2.18	110.11	2 females	2.45	93.5	7 females	2.1	114.86
Over 5 Pounds, Including 6 Pounds, 22 Cases			*9 Primiparas*			*13 Multiparas*		
	2.4	105.24		2.01	108.3		2.36	102.9
14 males	2.49	106.7	5 males	2.6	108.	9 males	2.42	104.9
8 females	2.21	103.9	4 females	2.2	108.75	4 females	2.22	99
7 Cases of 5 to 6 Pounds Group Listed as Premature			*6 Primiparas*			*1 Multipara*		
	2.34	115.43		2.4	117		2	104
4 males	2.68	116.5	4 males	2.68	116.5			
3 females	1.9	114	2 females	1.85	119	1 female	2	104
Over 6, Including 7 Pounds			*22 Primiparas*			*48 Multiparas*		
70 cases	2.31	109.85			111.4			109.6
31 males		107.07	9 males		115.1	22 males		103.33
39 females		112.05	13 females		108	26 females		114.09
Over 7, Including 9 Pounds			*53 Primiparas*			*127 Multiparas*		
180 cases	2.45	110.48		2.52	113.1		2.43	109.47
98 males		109.29	33 males		112	65 males		107.91
82 females		111.92	20 females		114.93	62 females		110.95
Over 9 Pounds, 60 Cases			*24 Primiparas*			*33 Multiparas*		
	2.59	108.8		2.6	111.88		2.59	106.79
36 males		106.73	16 males		112.31	19 males		103.05
24 females		111.88	8 females		111	14 females		111.86

In Table VI, intelligence quotients are classified according to maternal weight gain. The best IQ is in infants whose mothers gained 18 to 25 pounds (115.1); and a steady decrease is seen as the pregnancy gains increase (105.3 for gains over 35 pounds; 98.2 for multiparas). Personality ratings have the same trend, being best if the maternal weight gain was 18 pounds or under and worst if the increase was 30 to 35 pounds.

TABLE VI. MATERNAL WEIGHT GAIN

PERSONALITY RATING	IQ	BABY'S WEIGHT (POUNDS)	PERSONALITY RATING	IQ	BABY'S WEIGHT (POUNDS)	PERSONALITY RATING	IQ	BABY'S WEIGHT (POUNDS)
18 Pounds or Under, 72 Cases			*22 Primiparas*			*50 Multiparas*		
2.33	109.34	7.51	2.44	109.48	7.13	2.29	109.28	7.68
Over 18 Pounds, Through 25 pounds, 68 Cases			*31 Primiparas*			*37 Multiparas*		
2.34	115.1	7.82	2.35	115.2	7.72	2.34	115.01	7.89
Over 25 Pounds, Through 30 Pounds, 27 Cases			*8 Primiparas*			*19 Multiparas*		
2.48	108.75	8.23	2.06	112.57	8.16	2.64	107.34	8.26
Over 30 Pounds, Through 35 Pounds, 5 Cases			*2 Primiparas*			*3 Multiparas*		
3.3	107.2	7.61	2.95	101.5	6.13	3.5	111	8.6
Over 35 Pounds, 14 Cases			*8 Primiparas*			*6 Multiparas*		
2.72	105.3	8.52	2.87	109.7	8.28	2.53	98.2	8.83

It is of interest that the infant birth weights increase in all groups as the maternal gain increases (except the five cases listed under 30- through 35-pound gain and in this group one 4-pound premature infant distorts the average).

NO. OF CASES	GAIN IN POUNDS	NO. TOXIC	PER CENT TOXIC
72	18 or under	5	6.94
68	18 to 25	8	11.77
27	25 to 30	3	11.11
5	30 to 35	3	60.0
14	Over 35	1	7.14
Per cent toxic of entire series			10.38

Sex is another factor affecting IQ. In all the tables, the females have a higher IQ than the males except the 13 jaundice, 13 premature, and 6 eclamptic cases. (For the entire series, male IQ is 108.2 and female IQ is 112.12.) Unless the hereditary trait for the mentality is sex linked, the IQ should be equal. Possibly the differences in IQ could be explained by an increased vulnerability carried in the sex-determining chromosome for males. This is partly substantiated by the amount of difference in IQ for different types of delivery:

Spontaneous: Male IQ 3.42 points lower than female IQ
Forceps delivery: Male IQ 5.39 points lower than female IQ
Breech delivery: Male IQ 7.64 points lower than female IQ
Cesarean section: Male IQ 5.8 points lower than female IQ (5 of the 7 sections were performed upon toxic patients)

In larger series, the jaundice seen with Rh sensitivity is more disastrous to the male as far as death rate goes. The 13 jaundice cases in this study were born before Rh testing was done, and are too few to be significant.

Personality ratings for males show the opposite (by a narrow margin of 0.02 points). Since personality ratings include initiative, leadership, and industriousness, perhaps it is not surprising to find the males averaging higher here than in the IQ rating.

Skill of the obstetrician is another factor, as the average IQ of the children delivered by the one doctor having special obstetrical training was 113.06. The series average was 110.04. Personality rating was 2.39 in his group, less favorable than the 2.27 for the entire series.

In Table VII, a comparison of parity is made. For the first, second, and third born children the IQ is above average and almost equal. But in fourth, fifth, sixth (and up) children there is a steady drop in IQ to 103.78 for the children of grand multiparas (gravida vi and up). Personality ratings do not follow the same pattern. The surprising drop in IQ with increasing parity could be misleading if the poorer classes with supposed lower IQ are the only ones having 4 or more children. Therefore, a group of 44 first, second, and third born children known to come from families of four or more children were studied and found to have an average IQ of 109.93; comparing this with the parity table, they fit between the fourth and fifth born children, suggesting that larger families do average a lower IQ, but parity does have some effect as these first, second, and third born children have a higher IQ than fifth or later born children. Similarly, a group of 94 siblings were studied with these rather confusing results:

13 children of primiparas had IQs 13.32 points higher than siblings.
10 children of primiparas had IQs 11.16 points lower than siblings.
(Averaging these two groups, IQ of children of primiparas is 2.68 points higher.)

14 children of multiparas had IQs 14.14 higher than younger sibling.
18 children of multiparas had IQs 16.29 lower than younger sibling.
(These two groups average 2.98 points lower for older sibling.)

TABLE VII. EFFECT OF PARITY

GRAVIDA	IQ	PERSONALITY RATING	NUMBER OF CASES
1	112.53	2.55	147
2	112.17	2.36	94
3	113.8	2.41	48
4	110.72	2.41	25
5	108.81	2.33	24
6 and over	103.78	2.73	39

Two other factors not investigated were suggested by one infant who had bloody spinal fluid, having an IQ of 67; and by another whose mother had threatened to miscarry but successfully delivered a child whose IQ was later found to be 79.

Summary and Conclusions

An infant's IQ may be affected by factors related to pregnancy, labor, and the infant himself.

The pregnancy factors are as follows:

1. Eclampsia was found to result in IQ of 101.2.
2. Pre-eclampsia resulted in IQ of 105.89.
3. Maternal weight gains over 25 pounds progressively lower IQ (to 105.3 if mother gains over 35 pounds).

The factors of labor are as follows:

1. Labors over 30 hours result in IQ of 102; labors under one hour result in IQ of 105.8.
2. Increasing multiparity is associated with lower IQ, grand multiparas having children with IQ of 103.78.
3. Cases probably receiving Pituitrin had children with IQ average of 105.11.
4. Ether anesthesia resulted in IQ of 107.67.
5. Forceps deliveries resulted in IQ of 109.51.

Infant factors are as follows:

1. Weight: Babies over 5 through 6 pounds had an IQ of 105.24.
   Babies over 9 pounds had an IQ of 108.8.
2. Sex: Male IQ, 108.2; Female IQ, 112.12.

The IQ for the entire series was 110.04.

DIAGNOSIS AND MANAGEMENT OF RUPTURE OF THE UTERUS*

With a Study of 64 Maternal Deaths

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IN 1943 we[1] reported thirty maternal deaths from rupture of the uterus which had occurred in Brooklyn during the period, January, 1937, to September, 1942; fourteen additional cases in which this diagnosis was not proved, though highly probable, were not reported at that time. Since then, until January, 1948, twenty deaths from rupture of the uterus have occurred, eighteen of them proved. Since our first report presented but little clinical data, these thirty cases have been restudied and included in this series. The total number of cases, then, is sixty-four, in sixteen of which rupture of the uterus, though not proved, is believed to have occurred. All cases have been discussed by the Committee on Maternal Welfare of the Medical Society of Kings County.

In 48 cases the site of rupture was recorded. The upper segment ruptured in but 3 cases. In 45 cases rupture occurred entirely or principally in the lower segment, chiefly lateral, but in the anterior and posterior walls as well. In 16 cases in which rupture was not proved, it probably took place in the lower segment.

There were seven primiparas and 57 multiparas, with but one primipara in the spontaneous rupture group; 58 patients were white, and eight Negro.

On the basis of etiological factors, 27 are classified as spontaneous and 37 traumatic. Further subdivision follows:

Spontaneous Rupture.—	
"Grand multipara"	8 cases
Rupture of uterine scar	4 cases
Pituitary extract	4 cases
Obstructive dystocia, hydrocephalus	3 cases
Cervical scar	2 cases
Other	6 cases
	27 cases
Traumatic Rupture.—	
Version	20 cases
Forceps	9 cases
Craniotomy	3 cases
Fundal pressure	3 cases
Pinard maneuver	1 case
Bagging	1 case
	37 cases

Spontaneous Rupture

The "grand multipara."—The eight women in this group showed great multiparity. Brief case reports follow. All were proved to be ruptures of the uterus save Case 1.

*Read before the Brooklyn Gynecological Society, May 7, 1948.

CASE 1.—Aged 39 years, white, gravida v, para iv. Curettage was performed 10 months previously, with a diagnosis of chronic endometritis. The cervix had a deep scar which extended into the left vaginal fornix. Contractions were irregular for 4 days after rupture of the membranes, and then became regular and strong. After ten hours the baby and placenta were delivered in bed; shock followed. The uterus and vagina were packed for moderate hemorrhage. Death in shock one-half hour later.

CASE 2.—Aged 31 years, white, gravida viii, para vii. Admitted to the hospital at 7 months for vaginal bleeding. Labor began one week later, and after 2 hours, a 4 pound, 8 ounce live fetus was precipitated in bed. Postpartum hemorrhage of about 750 c.c. occurred. Examination disclosed no tear. Treated by uterine packing, transfusion, and repacking. Death three hours after delivery. Autopsy showed a laceration on the left, just above the cervix; it was but 3 cm. long and 0.75 cm. deep, yet a large vessel had been torn. The serosa showed an extensive hemorrhagic area, but the tear was incomplete.

CASE 3.—Aged 28 years, white, gravida viii, para vii. After eleven hours of labor she complained of pain in the right side of the abdomen and flank. Contractions ceased and she became cold and clammy. Fetal parts could be clearly outlined and the abdomen was very tender. No external bleeding. X-ray showed breech presentation though a definite vertex presentation had been noted on admission; no definite outline could be seen about the fetus. Hysterectomy was performed 4 hours after rupture was suspected. The abdomen was full of blood and contained the placenta. The fetus was lying in a rupture in the left lower uterine segment. Death nine hours after operation.

CASE 4.—Aged 40 years, white, gravida xv, para xiv. Pendulous abdomen. Slight vaginal bleeding after 14 hours of labor, followed by shock, cessation of pains, and loss of fetal heart tones. Though a vertex presentation on admission, vaginal examination now showed a foot presenting and placental tissue in the vagina. A diagnosis of placenta ablatio was made. Autopsy showed a rupture of the uterus.

CASE 5.—Aged 32 years, Negro, gravida ix, para viii. Admitted in labor with membranes ruptured for three days. Contractions occurred every seven minutes, but after three hours the cervix remained undilated. Eight minutes later precipitate delivery was followed by profuse bleeding and shock. Examination disclosed a tear of the cervix extending into the left broad ligament and peritoneal cavity. Hysterectomy six hours after delivery. Death two hours later.

CASE 6.—Aged 43 years, Negro, gravida ix, para viii. After two hours of labor, the patient had a very strong uterine contraction that caused the uterus to stand out. This was followed by cessation of labor, slight vaginal bleeding, loss of the fetal heart tones, and shock. The fetus was palpated directly beneath the abdominal wall. Patient died two hours later. Autopsy showed about 3,500 c.c. of blood in the peritoneal cavity with the fetus and placenta free. There was a rent in the right lower segment.

CASE 7.—Aged 41 years, white, gravida vii, para vi. Pre-eclamptic toxemia. Admitted to the hospital after fifty-eight hours of ruptured membranes and ten hours of labor. Fetal parts could be palpated with unusual ease and the fetal heart sounds were not heard. There was tenderness in both flanks. At operation, the fetus and placenta were free in the peritoneal cavity and there was an irregular tear anteriorly in the lower uterine segment. Hysterectomy was performed and 2,000 c.c. of blood were transfused during the next twenty-four hours. Death three days later with anuria.

CASE 8.—Aged 39 years, white, gravida vii, para vi. One eclamptic convulsion was followed by regular uterine contractions; nine hours later, labor ceased and shock followed. Forceps delivery failed. Examination revealed a rent in the posterior wall of the uterus. A second convulsion was followed by death. Autopsy showed a rent in the posterior wall of the lower segment of the uterus through which the fetal head and an arm protruded.

Spontaneous rupture of the uterus in the "grand multipara" is generally attributed to weakening of the uterus as a result of myometrial pathology. We believe cervical scarring to be an important and unappreciated factor. In Case 5, a cervix which was unchanged after three hours of labor suddenly yielded and permitted a precipitate delivery eight minutes later. The tear in the cervix was continuous with rupture of the lower uterine segment. Case 1 also had an extensive scar of the cervix. There are five other cases in this series which showed cervical scarring; in two, rupture was spontaneous, and, in 3, traumatic.

Pituitary Extract.—Four patients received posterior pituitary extract during the first stage of labor. It had also been administered to an occasional patient elsewhere in this series but in these four cases it appeared to be responsible for rupture of the uterus. Two of these patients had operative procedures prior to recognition of the rupture; in one case, clinical evidence of rupture was noted before interference.

CASE 9.—Aged 39 years, white, gravida vi, para iii, admitted at term with ruptured membranes. Mild irregular pains occurred for twenty-two hours. The fetal heart rate was normal, the cervix 3 cm. dilated and the vertex was at station minus 3. After six doses of 1 minim each of posterior pituitary extract at about 20-minute intervals, the patient became orthopneic and cyanotic. A diagnosis of rupture of the uterus was made and operation was performed one hour later. At operation, a rent was found in the posterior lower segment of the uterus extending into the right broad ligament with free and clotted blood in the right retroperitoneal space behind the cecum. Hysterectomy was performed and 3,000 c.c. of blood were given by transfusion. Death in shock two hours after operation.

CASE 10.—Aged 45 years, white, gravida iv, para iii, admitted to the hospital at term. A breech presentation was diagnosed. After twenty hours of labor the cervix was fully dilated, and contractions became weak and irregular. Two 5-minim doses of posterior pituitary extract within one-half hour increased the intensity of the contractions; 11 minims were given fifteen minutes after the second dose. Shock followed immediately. Vaginal examination showed a transverse presentation, and rupture of the uterus was diagnosed. At operation, the abdomen contained a large amount of blood and the placenta. A rent in the posterior surface of the uterus extended from the cervix to the fundus with a large hematoma beneath the bladder. The fetus was free in the peritoneal cavity with the hydrocephalic head and an arm still contained in the uterus. Hysterectomy was performed rapidly. Death from peritonitis on the fourth postoperative day.

CASE 11.—Aged 30 years, gravida iv, para iii, admitted to the hospital at term with weak and irregular pains. The umbilical cord and an arm prolapsed. They were reposited and the vertex pushed over the pelvic inlet. Following two 1-minim doses of posterior pituitary extract, contractions became strong and were followed by spurts of vaginal bleeding. The patient became pale and the pulse rapid. When a second examination revealed recurrence of transverse presentation, internal version was performed. She was treated for shock and improved. No contractions occurred despite twelve more doses of pituitary extract. She died of peritonitis on the fourth day, undelivered. Autopsy showed the abdomen to contain 3,000 c.c. of blood and the fetus. There was a rent in the lower segment through which the placenta protruded.

CASE 12.—Aged 33 years, white, gravida iv, para iii, admitted to the hospital in active labor. About 16 hours later "5 units" of posterior pituitary extract were given and an unsuccessful attempt at forceps delivery was followed by shock. At operation eight hours later, a large amount of blood and the fetus were found in the abdominal cavity. There was a tear 6 inches long in the right lower segment. Hysterectomy was performed with transfusion of 3,000 c.c. of blood. Death was due to hemorrhage and shock.

Posterior pituitary extract should not be administered to the grand multipara, or to any multipara if a dense cervical scar is thought to be present. Nor should it even be given in premature labor or if there is mechanical hindrance to delivery, like hydrocephalus or transverse presentation. Whenever administered, the dose should not exceed one-half minim, and one of us employs one-eighth minim, diluting the extract one minim to one c.c. of normal saline solution. The time interval between doses should not be less than thirty minutes.

Obstructive Dystocia—Hydrocephalus.—In three cases hydrocephalus was not recognized, causing obstructive dystocia followed by spontaneous rupture of the uterus and death.

CASE 13.—Aged 27 years, white, para ii. The cervix was fully dilated after ten hours of labor and there was little progress thereafter. One hour later, the pulse became rapid and feeble, and the blood pressure could not be obtained. Rupture of the uterus was not suspected. On vaginal examination a brow presentation was diagnosed. A stillborn hydrocephalic fetus was delivered by forceps with difficulty. Death one hour later.

CASE 14.—Aged 31 years, white, para iii. This patient had twelve hours of labor before the uterus ruptured. At laparotomy, a hydrocephalic fetus with spina bifida was found free in the peritoneal cavity. There was a rent in the lower segment and into the broad ligament. Subtotal hysterectomy was performed. Death four hours after operation was due to hemorrhage and shock.

CASE 15.—Aged 36 years, white, para v. Membranes ruptured one week prior to admission to the hospital. The fetus appeared large and there was no engagement of the vertex. Shock followed nine hours of active labor. At laparotomy, the body of the fetus was found free in the abdomen with a hydrocephalic head in the uterus. Hysterectomy was performed, and a transfusion given. Death from peritonitis on the fifth day.

Rupture of a Uterine Scar.—In four cases death was due to rupture of a scar in the upper uterine segment; in the seventh month of pregnancy in two cases, and in two cases at term. In three cases, cesarean section had been performed previously, and in one case myomectomy. In two cases in which the area of rupture was closed by suture, death was due to pulmonary complication, the result of general anesthesia in one case. In two cases, hemorrhage and shock caused death. Diagnosis was confirmed by autopsy or operation in three cases.

Other Causes.—In eight cases, rupture of the uterus was due to varied or unknown causes. Two patients had cervical scarring, two had numerous abortions and were elderly, and one had a markedly pendulous abdomen. A classic picture of spontaneous rupture including vaginal bleeding, disappearance of the fetal heart sounds, shock, a globular mass to the side of the fetus and fetal parts easily palpable beneath the abdominal wall was present in five patients. Diagnosis was confirmed in seven cases either at operation or autopsy. In five cases hysterectomy was performed. Death was due to hemorrhage and shock within twenty-four hours in five cases, peritonitis (one case) and pneumonia (two cases). A brief case report showing the role of cervical scarring follows:

CASE 16.—Aged 37 years, white, gravida iii, para ii. Her past history included a difficult forceps delivery with cervical laceration. She was admitted to the hospital near term for a slight painless and apparently causeless hemorrhage. Vaginal examination showed no placenta and the membranes were ruptured artificially. After sixteen hours of labor, she went into shock. The fetal heart tones disappeared, a globular mass was palpated in the

right side of the abdomen, and the fetal parts were easily palpable on the left. At operation, the fetus, placenta, and about 500 c.c. of blood were found free in the peritoneal cavity. The rupture in the lower segment involved the entire cervix, extending to the middle of the corpus. Death occurred during hysterectomy.

Traumatic Rupture

Version.—This procedure is the most common cause for rupture of the uterus, accounting for twenty deaths in this series. The secondary etiological factors in this group were transverse presentation, placenta previa, failed forceps, and ovarian tumor. Cases will be discussed under these subdivisions.

Transverse presentation: In eight cases transverse presentation was treated by internal version; extraction was prompt in every case but one. All were multiparas; five had ruptured membranes for more than thirty hours, and three of these were in labor for thirty-six hours or more. In many cases, although the cervix was not fully dilated at the time of version, extraction was performed. It is noteworthy that, although some reports described the ease with which internal version and extraction had been done, rupture of the uterus nevertheless resulted. The clinical picture of vaginal bleeding and shock out of proportion to the blood loss was constant, yet hysterectomy was performed in but two cases. Diagnosis was confirmed at operation or examination after death in five patients. One patient died of peritonitis on the third day, while the others died of hemorrhage and shock within twenty-four hours after rupture, four within three hours, indicating the speed with which uterine rupture can cause death. An illustration of this type of case follows:

Case 17.—Aged 32 years, white, gravida ii, para i, admitted near term and in labor. The presentation and position of the fetus were not definitely determined. After forty hours of labor with membranes ruptured for thirty-one hours a fetal arm was noted protruding through the vulva. Under ether anesthesia, internal version and extraction of a 6 pound, macerated fetus were performed. Shock, with but slight vaginal bleeding, followed this procedure. It was felt inadvisable to operate because of her poor general condition, and small amounts of blood were transfused. Death occurred twenty-four hours after delivery. Autopsy showed intraperitoneal hemorrhage and a ragged tear in the left lower uterine segment.

Placenta previa: In six cases, placenta previa had been treated by internal version and extraction. In no case was there evidence that the cervix was fully dilated before extraction, and, in fact, in one case the type of version was Braxton Hicks. All patients died of hemorrhage and shock, five within a few hours of delivery. It is well accepted that when Braxton Hicks or internal version is performed for placenta previa, it is hazardous to attempt extraction because of the friability of the lower uterine segment. As a matter of fact, since studying 50 deaths from placenta previa in Brooklyn,[2] we are convinced that in treatment of placenta previa, Braxton Hicks and other forms of version should be abandoned.

Failed forceps: In five cases, rupture of the uterus was due to internal version and extraction performed after attempts at forceps delivery had failed. In four cases, 34 to 52 hours of labor preceded the delivery. A retraction ring was present, and the cervix incompletely dilated in three cases. Forceps application was high in four cases. Diagnosis was proved in four cases, one by examination and three at autopsy. In two of the latter, exploration of the uterus before death had failed to reveal the rupture. Death was due to peritonitis in three cases and to shock in two cases.

Ovarian tumor:

CASE 18.—Aged 28 years, white, gravida ii, para i. After fifty-eight hours of labor and although the cervix was not fully dilated, a difficult internal version and extraction were performed. Hemorrhage and shock followed. Examination showed a tear in the lower uterine segment anteriorly, extending from one broad ligament to the other. A mass which proved to be a dermoid cyst of the ovary was felt. After uterine packing and transfusion, hysterectomy and oophorectomy were performed. Death on the following day of hemorrhage and shock.

Forceps.—Nine patients had forceps application followed by attempts at, or actual, forceps delivery which resulted in rupture of the uterus. In the etiological factors noted were two cases of cervical scarring, one case of placenta previa, and three persistent occipital posterior positions. Two patients died undelivered because of failed forceps. Three had forceps rotation, one by the Scanzoni maneuver. In the placenta previa case, a cervix dilated only 3 cm. was incised laterally before forceps extraction. Severe shock with but moderate vaginal bleeding was noted in nearly every case. The diagnosis was proved in six cases. Two patients were treated by packing and one by hysterectomy. Eight patients died of hemorrhage and shock within nine hours, and seven within three hours. One patient died of peritonitis eight days after delivery.

Craniotomy.—Three patients died following craniotomy. In two cases, forceps extraction had failed. Diagnosis was confirmed at autopsy in two patients who died of hemorrhage and shock within one hour after delivery.

Fundal Pressure.—In three cases, rupture of the uterus was the result of strong fundal pressure. In two there was impaction of the shoulders of fetuses weighing 11½ and 14 pounds. All ruptures were proved. Death was due to anesthesia for hysterectomy (one case), hemorrhage and shock (one case), and peritonitis (one case). A case report follows:

CASE 19.—Aged 41 years, gravida iii, para ii. Delivery was attempted at home by strong fundal pressure after full dilatation of the cervix. Slight vaginal bleeding, rapidity of the pulse, and sudden cessation of pains followed. On admission to the hospital, there was considerable distention of the abdomen with a large globular mass on the right and another mass in the left lower quadrant of the abdomen. The caput was showing, fetal heart tones were absent, and the patient was vomiting. A diagnosis of rupture of the uterus was made. At operation the abdomen was full of blood due to rupture of the left lower segment of the uterus with tearing away of the broad ligament. While the fetus was delivered from below, hysterectomy was performed. Vomiting and aspiration during general anesthesia caused death.

Pinard Maneuver and Bagging.—

One patient had a Pinard maneuver for a breech presentation complicated by placenta previa. A 9 pound, stillborn infant was partially extracted. Hysterectomy was performed for rupture of the uterus, with death from hemorrhage and shock on the operating table. The second patient had many complications including toxemia of pregnancy, jaundice, premature separation of the placenta, and intrapartum infection. Treatment consisted of bagging, administration of posterior pituitary extract, and forceps delivery. Incomplete rupture of the uterus caused hemorrhage and shock. Death on the day of delivery.

Diagnosis

When the uterus ruptures during labor, its recognition should be easy, yet diagnosis is often missed or unduly delayed, partly because rupture occurs but rarely in the experience of any individual, and perhaps because the

obstetrician fears that he may open the abdomen in error. Procrastination is in fact the most important cause of death. Except in the case of the grand multipara, threat or imminence of rupture should be recognized.

In persistent brow, face, and scapular presentations, spontaneous delivery can occur only under unusual circumstances. When there is an obstacle to delivery, whether it be a pelvic tumor or hydrocephalus, when the cervix is fully dilated and the vertex remains unengaged in spite of increasing frequency and intensity of uterine contractions, and when the lower segment is thinly stretched up to a pathological retraction ring, rupture of the uterus threatens. The appearance and behavior of the patient will point to the gravity of the situation.

At that time, sudden and complete relief of the pain of labor with cessation of uterine contractions is evidence of uterine rupture. Vaginal bleeding is significant, though not often sufficiently great to account for deepening anemia and shock. Vaginal examination and abdominal palpation may show recession of the presenting part or actual change of pole, and the fetus itself may be easily felt outside a hard contracted uterus. However, the fetus may not escape from the uterus or may be fixed deep in the birth canal, and, in fact, may be delivered alive. Fetal heart tones may not be lost at once and symptoms of intraperitoneal hemorrhage may be delayed for several hours.

When rupture of the uterus is the result of trauma incident to internal version, with or without breech extraction, forceps delivery or craniotomy, diagnosis is most often missed. Not because diagnosis is difficult to make, but it is assumed that hemorrhage and shock are due to trauma and anesthesia, and not to rupture.

When hemorrhage and shock follow a major vaginal operative procedure, the uterus should be explored. Exploration is indicated after internal version and after any delivery in which shock appears to be an inconsistent sequel. The danger incident to examination of the uterine cavity is far less than the risk of delay or failure of diagnosis. If rupture of the lateral uterine wall is not found, the anterior and posterior walls should be examined with special care.

Management

Impending rupture of the uterus demands immediate treatment. Tetanic contractions of the uterus may be fairly controlled by administration of ether or chloroform during preparation for delivery. If vaginal delivery is practicable, any operative procedure must be performed with utmost gentleness and care. Internal version is absolutely contraindicated. No attempt should be made to dislodge the presenting part or to thrust the fetus upwards as these procedures will probably result in rupture of the excessively thinned-out lower segment. If forceps are applied to the vertex, the blades must be introduced carefully, and if slight trial traction fails to bring about advance no further test may be made. At times, perforation of the head is preferable. If cesarean section is elected, hysterectomy may be necessary.

As a rule, complete rupture of the uterus will result in death unless adequate treatment be instituted within a few hours. The cardinal principles of good treatment are massive transfusion and immediate operation. When rupture has occurred through a previous cesarean section scar, excision of the old scar and resuture, if feasible, is preferred. If the uterine laceration is irregular and raggid, then supravaginal hysterectomy will be necessary. The operation should be performed with speed and gentleness with little attention to refinements of technique. In apparently hopeless cases, opera-

tion may consist only of rapid excision of the uterus between broad ligament clamps and abdominal closure with through and through interrupted sutures; the clamps may be removed on the third day.

In the event of rupture of the uterus with the presenting part low in the birth canal, extraction of the fetus is definitely contraindicated. Though vaginal delivery may in rare cases save the fetus, it enlarges the tear, increases hemorrhage, wastes valuable time, and markedly lessens the patient's chance for recovery.

If rupture of the lower uterine segment is minimal and known to be incomplete and hemorrhage into the broad ligament and parametrium is not great, rupture may be repaired from below. If there is any doubt about complete control of hemorrhage, the abdomen should be opened at once. Tamponade may at times be satisfactory, but it is not advised.

In almost every case, transfusion spells the difference between life and death. As a rule, less then 1,000 c.c. is futile, and it may be that 3,000 c.c. or more of blood will be required. If, as is advised, 1,000 c.c. of compatible blood are available on every delivery floor, this will tide the patient over until more is obtained. It may be wise to make use of more than one venous portal for transfusion. Femoral veins are practical avenues for transfusion of blood and much better than time-consuming and often futile cutdown upon collapsed veins elsewhere.

Summary

1. The clinical data of sixty-four deaths from rupture of the uterus are presented; twenty-seven were spontaneous and thirty-seven were the result of trauma.

2. In all but three cases, rupture took place in the lower segment of the uterus. The role of cervical scarring in the etiology of rupture is emphasized.

3. Internal version is the most frequent cause and should be recognized as an extremely hazardous procedure under certain unfavorable conditions.

4. That strong fundal pressure can rupture a uterus is shown by three cases in this series.

5. Four deaths occurred from the use of pituitary extract during the first stage of labor. Despite this, the judicious use of minute doses in carefully selected cases of uterine inertia is advised.

6. The diagnosis of rupture of the uterus is often not made sufficiently early for survival of the patient. Routine exploration of the uterus after traumatic vaginal procedures is indicated, especially if shock is present.

7. The essence of adequate treatment for complete rupture of the uterus is prompt massive blood transfusion and hysterectomy. Shock is no contraindication to operation.

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STATISTICAL STUDY OF CHORIONEPITHELIOMA IN THE PHILIPPINE GENERAL HOSPITAL

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THIS is a continuation of the studies on chorionepithelioma begun since Acosta-Sison et al.[1] published the first 6 cases that recovered. Interest in the subject started only in 1936, and up to Dec. 15, 1941, we have gathered for study 72 cases.[2] From Dec. 16, 1941, to Dec. 31, 1946, we have admitted to the Philippine General Hospital 70 cases, making a total of 142 cases. Only one case was seen in the last two weeks of 1941, so that 69 cases were admitted in five years (1942-1946), giving an average of over thirteen cases per year. We admit that this incidence is very high when compared to that of London Hospital as presented by Brew,[3] who found only 24 cases in 52 years (1885 to 1937) an average of one case every two years. We have no explanation for this, just as we cannot explain why we have a very high incidence of hydatidiform mole. Acosta-Sison et al.[4] gave an incidence of hydatidiform mole in the Philippine General Hospital of one for every 126 pregnancies, in contradistinction to Mathieu's[5] figure which is one for every 2,000 pregnancies. All we can say is that though both conditions are found in primigravidas they are more common in multigravidas and multiparas, and Filipino women are very prolific, having as many as 19 pregnancies. It seems that the frequent subjection of the individual to pregnancy, especially if the pregnancies rapidly succeed one another, but more especially if they terminate in the early months as abortion or mole, favors the development of chorionepithelioma. To this we have to add that Philippine General Hospital is what may be called the wastebasket of pathologic cases, especially obstetrical ones.

TABLE I. INCIDENCE OF CHORIONEPITHELIOMA ACCORDING TO GRAVIDITY AND PARITY 70 CASES*

	NO. OF CASES	
Gravida i to gravida ii	10	27 cases
Gravida i, para i	2	
Gravida ii, para i	8	
Gravida ii, para ii	1	
Gravida iii, para ii to gravida v, para iii	6	
Gravida vi, para iv	9	43 cases
Gravida vi, para v to gravida ix, para vii	16	
Gravida ix, para viii to gravida x, para ix	7	
Gravida xii, para ix to gravida xvii, para xi	5	
Gravida xiv, para xiii to gravida xix, para xiv	6	

*Of the 70 cases, only three had had neither abortion nor hydatidiform mole. In ten cases, or in 14.28 per cent, the pregnancies did not reach beyond three months. Only ten patients, or 14.28 per cent, were primiparas; the rest were multigravidas and multiparas.

Table I shows that 27 cases of chorionepithelioma developed in women who had from one to not more than five pregnancies, three of which resulted in full-term babies, whereas 43 out of 70 cases of chorionepithelioma developed in women who were gravida vi, para iv to gravida xix, para xiv. The same table also shows that ten cases, or in 14.28 per cent of all the pregnancies of the women affected, did not reach beyond three months. The table further shows that only three out of 70 women had neither abortion nor hydatidiform mole.

One question to which we wanted to find the answer was whether there was correlation in the age incidence of parturition, abortion, hydatidiform mole, and chorionepithelioma; hence the formation of Table II which shows that the greatest age incidence of parturition, 59.35 per cent, is in the third decade, between the ages of 20 and 29 years. The same is true with hydatidiform mole, though the percentage is lower, 44.52 per cent. But the greatest age incidence of abortion, 54.71 per cent, is in the fourth decade, 30 to 39 years. The same is true with chorionepithelioma, though the percentage is lower, 39.06 per cent. In the fifth decade, 40 to 46 years, the percentage incidence of parturition was only 3.72; abortion, higher than parturition, 11.32 per cent; hydatidiform mole, higher than abortion, 13.86 per cent; and chorionepithelioma, higher than mole, 18.74 per cent. From 50 to 52 years, there were no cases of parturition nor of abortion but there were one case (0.72 per cent) of hydatidiform mole and two cases (3.12 per cent) of chorionepithelioma.

TABLE II. RELATIVE INCIDENCE OF PARTURITION, ABORTION, HYDATIDIFORM MOLE, AND CHORIONEPITHELIOMA ACCORDING TO AGE

	APRIL 5, 1945 TO APRIL 5, 1946				JAN. 1, 1940 TO DEC. 31, 1943		DEC. 16, 1941 TO DEC. 31, 1946	
	PARTURITION		ABORTION		HYDATIDIFORM MOLE		CHORIONEPITHELIOMA	
AGE (YEARS)	NO. OF CASES	PERCENTAGE	NO. OF CASES	PERCENTAGE	NO. OF CASES	PERCENTAGE	NO. OF CASES	PERCENTAGE
15 to 19	34	6.06	7	6.60	23	16.71	6	9.37
20 to 29	333	59.35	29	27.35	61	44.52	19	29.69
30 to 39	173	30.83	58	54.71	33	24.08	25	39.06
40 to 46	21	3.72	12	11.32	19	13.86	12	18.74
50 to 52	0	0			1	0.72	2	12
Unknown age							6	

Table II, then, shows that the optimum age for pregnancies to reach full-term is between 20 and 29 years. However, hydatidiform mole has also its greatest incidence during this age period. The fourth decade (30 to 39 years) has the peak incidence of both abortion and chorionepithelioma, exceeding that of parturition. And after the age of 40, the percentage incidence of abortion, mole, and chorionepithelioma far exceeds that of parturition. It is interesting to note also that before the age of 20 years the percentage incidence of abortion, mole and chorionepithelioma slightly exceeds that of parturition.

All concede that over 50 per cent of chorionepitheliomas develop from hydatidiform mole.

Table III demonstrates that the type of pregnancy giving rise to chorion-epithelioma in two different series studied, namely, 70 cases from Dec. 16, 1941, to Dec. 31, 1946, and an earlier study of 72 cases[2] up to Dec. 15, 1941, give about the same percentage. Hydatidiform mole was the antecedent of chorionepi-thelioma in 62.85 per cent and 62.5 per cent, respectively; abortion in 24.28 per cent and 23.61 per cent, respectively; labor in 10 per cent and 11 per cent, respectively.

TABLE III. TYPE OF PREGNANCY GIVING RISE TO 70 CASES OF CHORIONEPITHELIOMA FROM DEC. 16, 1941, TO DEC. 31, 1946

	NO. OF CASES	PERCENTAGE	PERCENTAGE INCIDENCE OF PREVIOUSLY REPORTED 72 CASES UP TO DEC. 15, 1941
Hydatidiform mole	44	62.85+	62.5
Abortion	17	24.28+	23.61
Twins			
a. Mole			
b. 4 month fetus and normal placenta	1	1.42	
Miscarriage	1	1.42	
Premature labor 2 / Full-term labor 5	7	10.00	11

In a study of 136 cases of mole, Acosta-Sison et al.[4] have found that 30 cases, or 22.05 per cent, became malignant. This is a much higher percentage than the 5 to 16 per cent of malignancy from hydatidiform mole as given independently by Sunde and Findley who were cited by Stander.[6] It is not surprising that hydatidiform mole is the most common source of chorionepithelioma for the main pathology of hydatidiform mole is not so much the cystic degeneration of its mesodermic core, though this exists, as the undue proliferation of its epithelial elements, the Langhans' and syncytial cells, which, because of their excessive hormone formation, render the uterus with its enlarged vessels easily susceptible to their invasion and growth. In abortion, from which arises over one-fifth of the cases of chorionepithelioma, the epithelial elements of the chorionic villi are also quite active, in contradistinction to their condition toward full term, when senility of the placenta begins to make headway. Moreover, after the fifth month, the Langhans' cells not being needed any more become hyalinized and disappear. It may be that in the few cases of chorionepithelioma that develop after full term the Langhans' cells have persisted so that eventually they become abnormally active.

The method of diagnosis as given in the literature is the presence of chorionepithelioma cells in the diagnostic curettage or in the positive Aschheim-Zondek or Friedman test after the expulsion of the product of conception. When either or both of these tests are positive, they are of great help in arriving at a diagnosis. But we had at least two cases which consistently gave a negative diagnostic curettage on more than one occasion and in which the true nature of the disease was not discovered until laparotomy was made because of internal hemorrhage which was thought to be due to ruptured tubal pregnancy.

With regard to Aschheim-Zondek or Friedman Test, our experience is that they are often negative in cases of early chorionepithelioma. We had one case that had a negative Friedman test four months after an abortion from which the chorionepithelioma developed. Schuman,[8] in discussing McLaughlin's paper on mole followed by chorionepithelioma, cites his own case where the Aschheim-Zondek test was negative for one year. The test became positive only one month before the patient died. Chesley et al.,[9] in their studies on hydatidiform mole, report a case that developed chorionepithelioma in which the Friedman test was negative on the twenty-second day after the expulsion of the mole. On the other hand, they had cases of benign mole that did not develop chorionepithelioma in which the Friedman test was positive as long as over seven months after the expulsion of the mole. Hamburger[10] also reports that, in a follow-up study of 72 cases of hydatidiform mole, 9 per cent gave positive Friedman tests three months after the evacuation of the uterus, in spite of the fact that they did not develop chorionepithelioma.

We have employed with success the HBEs method as introduced by Acosta-Sison.[11] The method is nothing but the careful interpretation of the combined history, symptomatology, and physical findings. Since all our cases gave a history of having expelled the product of conception, from a few days, weeks, or months, to as long as three or more years before, and had complained of abnormal uterine bleeding, and on bimanual examination showed enlargement and softening of the uterus, the method was labelled as HBEs for short. Histology and the laboratory animal for hormonic determination were also used at times. The former was used always for confirmation of the diagnosis after hysterectomy or at autopsy.

We routinely send the pathologist the last curettings of every case of hydatidiform mole and of incomplete abortion for detection of malignancy. For this method, we employed the term "early microscopy" to distinguish it from what is ordinarily called diagnostic curettage or the curettage done for the purpose of determining the cause of any uterine bleeding occurring sometime after the expulsion of the product of conception.

The Aschheim-Zondek or Friedman test was used in combination with the other methods of diagnosis or in the follow-up of cases operated upon, wherein it is most valuable.

TABLE IV. METHOD OF DIAGNOSIS IN 70 CASES

	NO. OF CASES
HBEs positive and used as basis of diagnosis	43
3 of these were reported as malignant by early microscopy but operation was postponed until 1 month after the dilatation and curettage because of youth of the patients.	
1 was reported as benign by early microscopy.	
1 was reported as negative for chorionepithelioma by diagnostic curettage.	
All these 43 cases showed chorionepithelioma grossly and microscopically in the hysterectomized uterus.	
HBEs positive but preoperative diagnosis by another physician was uterine myoma	1
HBEs positive and the chorionepithelioma was confirmed at autopsy; not operated upon	1
HBEs positive but the positive diagnosis by diagnostic curettage was the basis of diagnosis	8
HBEs positive but preoperative diagnosis was ruptured tubal pregnancy	3
HBEs positive but preoperative diagnosis was cancer of the corpus uteri. Correct diagnosis was established only after biopsy of the hysterectomized uterus	2
Diagnosed as malignant mole because of marked discrepancy in the enlargement of the uterus as related to the length of amenorrhea	1
Hysterectomy was done with the mole in situ. Biopsy showed malignant mole.	
By early microscopy	11

Table IV shows that 43 cases have been diagnosed by HBEs. Three of these had been previously reported as malignant by early microscopy but because of the youth of the patients the operation was withheld, hoping the pathologist committed an error. But at the end of five weeks, HBEs was present, so the three patients were finally hysterectomized, although one was reported as benign mole by early microscopy, and one was reported negative for malignancy by diagnostic curettage. All the 43 cases showed chorionepithelioma grossly and microscopically in the hysterectomized uterus. In sixteen cases, HBEs was present but was not used as basis of diagnosis. The diagnosis in one case was uterine myoma; in three cases, ruptured tubal pregnancy; in two cases, cancer of corpus uteri. The correct diagnosis was made only at biopsy of the hysterectomized uterus. In eight cases, diagnostic curettage was used as the basis of

diagnosis. In one case, the hydatidiform mole was diagnosed as malignant because of the marked discrepancy between the size of the uterus (7 months) and the length of amenorrhea (2 months) and hysterectomy was done with the mole in situ. Biopsy showed malignant mole. Early microscopy was the basis of diagnosis in eleven cases. The hysterectomized uteri of all these patients showed foci of chorionepithelioma.

In the Philippines, where chorionepithelioma is not infrequent and where many lives on its account have been lost, one cannot emphasize the necessity of early radical treatment before metastasis occurs. And this necessarily involves early diagnosis. The steps we have taken to attain this are to examine histologically the last curettings of every case of mole or incomplete abortion for malignancy; then every patient curetted for mole is instructed to return to the hospital any time she has abnormal bleeding or, in its absence, after four to six weeks, when HBEs method may be applied.

TABLE V. MANAGEMENT OF 70 CASES OF CHORIONEPITHELIOMA

	NO. OF CASES
Hysterectomy (total or subtotal)	64
In 38 cases unilateral or bilateral salpingo-oophorectomy was also performed because of the involvement of the ovaries.	
In 4 cases the uterus was perforated and there was hemoperitoneum.	
In 1 case hysterectomy was done with the mole in situ. Histopathology showed malignant mole.	
In 4 cases the hysterectomy was followed by x-ray. 1 of these, in spite of complete hysterectomy followed by x-ray, developed vaginal metastasis from which the patient died.	
Not operated upon because of advanced metastasis in brain and lungs, confirmed by autopsy	4
Not operated upon because of advanced vaginal metastatic growth. X-ray and radium treatment proved futile. (Died of hemorrhage from vaginal growth)	1
Refused operation and eventually died at home	1

Table V shows that hysterectomy, total or subtotal, was performed in 64 cases. This was accompanied by unilateral or bilateral salpingo-oophorectomy in 38 cases where one or both ovaries had been affected. In 4 of the hysterectomized cases the uterus was found to be perforated by the growth and there was much hemoperitoneum. In one case, hysterectomy was done with the mole in situ. Histology of the uterus showed malignant mole. In four cases, the hysterectomy was followed by x-ray treatment because of incomplete removal of the chorionepithelioma cells at the broad ligament. One of these cases, in spite of complete hysterectomy followed by deep x-ray treatment, developed extensive vaginal metastasis from which the patient died. Four cases were not operated upon because of advanced metastasis in the lungs and brain, confirmed at autopsy. One case was also not operated upon because of advanced parametrial and vaginal metastasis when the patient was first seen. X-ray and radium treatment in this case proved futile. The patient died of hemorrhage from the vaginal growth. One woman refused operation and x-ray treatment and she eventually died at home.

TABLE VI. SITE OF PRIMARY GROWTH

Endometrium with extension to myometrium	58 cases
Myometrium with extension to endometrium	5 cases
Myometrium alone	8 cases
7 of these patients died. In 4 of those that died, there was uterine perforation with hemoperitoneum.	

Site of the Primary Growth.—As is to be expected, the endometrium was the part most frequently involved. Table VI shows that it was the site of primary growth in 58 cases, or 82.85 per cent. This is fortunate in the sense that when the endometrium is the primary site of the growth, uterine bleeding comes earlier and this may lead the patient to consult the physician earlier and such a growth is one amenable to the correct diagnosis by a diagnostic curettage. In twelve cases, the myometrium was the primary site. In five of these cases, there was extension of the growth into the endometrium. But, in eight cases, the endometrium was free from the growth so that a diagnostic curettage would render a negative finding of the growth. This was the result in those cases so operated upon, giving the physician and the patient a sense of false security. Seven of the myometrial cases died. In four of them, the uterus was perforated so that there was much hemoperitoneum causing the fatality.

TABLE VII. SITES OF METASTASIS

Lungs	7 cases
Lungs and brain	4 cases
Parametrium	3 cases
Vagina and parametrium	2 cases
Vagina	3 cases
Broad ligaments	4 cases

Sites of Metastasis.—As in a previous study made of 72 cases,[1] the lungs, vagina, and brain were found to be the most frequent sites of metastasis.

Table VII shows that among 70 patients there was metastasis in the lungs in eleven cases, in four of which there was also a concomitant metastasis in the brain. The parametrium was involved in five cases, in two of which the metastasis had extended into the vagina. Metastasis into the broad ligaments was found in four cases.

The metastasis into the lungs, brain, and the lower vaginal canal is carried by the blood stream, whereas the affection of the broad ligaments, parametrium, and upper part of the vagina must have taken place by the extension of the growth into these regions.

TABLE VIII. CONDITION OF THE OVARIES AS FOUND ON LAPAROTOMY OF 64 CASES

In 38 cases, 59.37 per cent, the ovaries were either cystic or were converted into ovarian cysts.
In 1 case, both ovarian cysts were the size of a grapefruit.
In 8 cases, both ovarian cysts were the size of an orange.
In 10 cases, both ovaries were cystic.
In 11 cases, only the right ovary was cystic.
In 8 cases, only the left ovary was cystic.

The ovaries, as shown in Table VIII, were found either to be cystic or to have been converted into cysts in 38 cases, or 59.37 per cent, of the 64 patients laparotomized. In eight cases, both ovaries had been converted into ovarian cysts having the size of an orange. In one case, both ovarian cysts were as large as a grapefruit. It is said that the cystic condition of the ovaries or their conversion into ovarian cysts is due to their abnormal hormonic stimulation from the chorionic cells of either the hydatidiform mole or chorionepithelioma and that the eradication of either brings about their recession. However, we saw at least three cases of hydatidiform mole where the concomitant ovarian cysts not only did not disappear but grew much bigger and these cases of hydatidiform mole did not develop chorionepithelioma.

TABLE IX. MORTALITY

OF THE 70 PATIENTS, 17, OR 28.57 PER CENT, EITHER DIED OR WENT HOME IN SERIOUS CONDITION	
CAUSE OF DEATH	NO. OF CASES
Hemorrhage after curettage (no donor)	1
Hepatitis and pyelonephritis after healed wound from hysterectomy. Patient was transfused with blood from a donor who had a history of malaria	1
Sudden death after healing of abdominal wound. Death unexplained by autopsy	1
Perforation of uterus by the growth with much hemoperitoneum; 1 of these was complicated by peritonitis	4
Peritonitis due to concomitant double pyosalpinx	1
Metastasis, broad ligament and lungs. Lung metastasis looked like miliary tuberculosis. Died soon after diagnostic curettage (not laparotomized)	1
Metastasis, lungs and brain (3 of these were not operated upon)	4
Metastasis, parametrium and vagina, extensive. (1 developed metastasis after panhysterectomy followed by x-ray)	2
Metastasis, lungs, extensive (not operated upon)	2

Table IX shows that the mortality of the 70 cases was 17, or 28.57 per cent. Nine deaths were due to extensive metastases. One death was caused by hemorrhage after dilatation and curettage for what was supposed to be incomplete abortion but which on biopsy turned out to be chorionepithelioma. No donor was then available. Nine of the 17 patients were hysterectomized. One of these patients died of hepatitis and pyelonephritis (autopsy findings) after blood transfusion from a donor who gave a history of malaria. The abdominal wound of this case healed by first intention. One patient died suddenly after the healing of the abdominal wound by first intention. Death in this case could not be explained by autopsy. Three patients died of intra-abdominal hemorrhage because of perforation of the uterine wall by the growth. One patient died of peritonitis because of concomitant bilateral pyosalpinx. The uterus of this case was also perforated. One patient died a few days after the diagnostic curettage. Autopsy showed extensive chorionepithelioma in the uterus, metastasis in both broad ligaments, and diffuse metastasis in the lungs looking like miliary tuberculosis. Microscopic examination of the lungs showed diffuse infiltration of Langhans' and syncytial cells. I believe that the miliary tubercular-looking metastasis in the lungs of this patient was provoked by the diagnostic curettage. HBEs was clearly present and diagnostic curettage should not have been employed. This case was not laparotomized.

The main causes of death were the extensive metastases and hemorrhage from the growth. However, early extirpation of metastasis in the lower part of the vagina, if localized, results in cure. The same may be said with the early metastasis in the lungs when promptly treated by x-ray. We cannot say the same with regard to the metastasis in the brain, for the four cases of brain metastasis in conjunction with metastasis in the lungs in this study of 70 cases, and the ten cases of brain metastasis in a previous study of 72 patients were all fatal.

The only hope for cure of chorionepithelioma is its early recognition and complete eradication before metastasis occurs.

Assertion had been made that extirpation of the primary growth, say in the uterus, brings about the recession of metastasis in other parts of the body. This claim has not been substantiated in our cases. The foci of chorionepithelioma, wherever they may be, and be they primary or metastatic, should always be completely eradicated surgically, if accessible, and by x-ray, if inaccessible to the knife. And this must be done early if the patient is to survive.

Summary

An analysis of 70 cases of chorionepithelioma admitted from Dec. 16, 1941, to Dec. 31, 1946, is presented. In addition to the 72 cases previously reported, this makes a total of 142 cases.

Tables of the most frequent age incidence, type of pregnancy that gives rise to chorionepithelioma, the sites of primary growth, the sites of metastasis, methods of early diagnosis, condition of the ovaries, and causes of mortality are discussed.

Attention is called to the limitation and even danger of diagnostic curettage in certain cases as a means of diagnosis. Its verdict when positive may be true but when negative does not necessarily mean absence of malignancy. The HBEs method should then be used, supplemented, if desired, by hormonic determination.

Early microscopy and the follow-up of every case curetted for hydatidiform mole will help to detect the early cases.

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HYDATIDIFORM MOLE FOLLOWED BY POSTPARTUM ECLAMPSIA AND CHORIONEPITHELIOMA, WITH RECOVERY

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THE relationship of hydatidiform mole to chorionepithelioma has been the subject of frequent dissertations in medical literature during the past years. However, little mention has been made of the toxemia that is sometimes associated with mole.

In a recent extensive survey of the world literature, Chesley, Cosgrove, and Preece[1] were able to collect only thirty-five cases of probable or alleged eclampsia occurring in association with hydatidiform mole. Only three cases in this series recorded convulsive seizures occurring in the puerperal period.

The authors recently had occasion to treat for hydatidiform mole a patient who developed convulsive seizures on her sixth postpartum day. The convulsions occurred in the presence of an elevated blood pressure, an albuminuria, and edema; and the convulsions were typical of those seen in eclampsia. Recovery was prompt with the usual medical treatment. Four months later the patient developed chorionepithelioma of the uterus, confirmed by surgery. The patient has remained in good health for one year postoperatively, and she shows no evidence of metastases or recurrences.

A complete report of the case is herewith presented:

The patient was a 29-year-old, white, secundigravida whose last normal menstrual period had begun on Nov. 17, 1946. Shortly thereafter, she developed nausea with occasional vomiting, which persisted until the end of February, finally disappearing without treatment.

On Jan. 17, 1947, the patient noted slight, brownish, odorless staining from the vagina, unassociated with backache or cramps. This recurred almost daily, but was never sufficient to necessitate the use of a pad.

Her past history was negative except for a spontaneous complete abortion at two months' gestation, April, 1945.

On March 17, the patient had a profuse vaginal hemorrhage associated with slight cramps and backache. Estimated blood loss was 500 c.c. On March 22, at 5 P.M., the patient had another profuse hemorrhage of approximately 500 c.c., and a similar hemorrhage occurred at 7 P.M. She was admitted to St. John's Hospital shortly thereafter.

On physical examination, the patient appeared extremely pallid. Blood pressure was 180/124, rectal temperature 99.6° F., pulse 108, respirations 20. On abdominal examination, the uterus seemed enlarged to 6 months' gestation, extending two fingerbreadths above the umbilicus. No fetal heart tones could be heard. Palpation of the uterus resulted in further profuse vaginal bleeding. Sterile vaginal examination revealed a well-formed, long cervix which would admit only one finger. The cervix seemed to be pushed anteriorly by a huge, soft, boggy mass filling the entire cul-de-sac. The palpating finger, when inserted into the cervix, encountered a boggy, spongy mass which seemed to cover the entire cervical os. The patient was prepared at once for laparotomy. The pre-operative diagnosis was placenta previa centralis.

Blood loss following admission to the hospital was estimated to be 1,200 c.c. Two pints of whole blood were given to the patient during the operative procedure, having been preceded by three 500 c.c. units of plasma.

At operation, the uterus was opened by a classical incision and a gush of grapelike clusters of hydatidiform mole escaped through the incision. The uterus was completely evacuated, and the endometrial cavity was wiped clean with laparotomy pads. There was no evidence of invasion of the uterine wall. No fetus or placenta could be demonstrated.

Pathologic study of the specimen was reported as typical of hydatidiform mole, both grossly and microscopically.

The patient responded well to the usual postoperative measures, and her convalescence seemed relatively uneventful. On the first postoperative day, the hemoglobin was found to be 13 per cent or 2.2 Gm. Replacement therapy of whole blood by transfusion was continued. The blood pressure remained at 140/90.

On March 26, the hemoglobin was 74 per cent or 11.4 Gm. The carbon dioxide combining power was 54 per cent. Blood urea nitrogen was 13 mg. per cent, and the blood chlorides were 480.

On March 28, during her morning bath, the patient was suddenly seized by a generalized convulsion which lasted five minutes. A second convulsion lasting three minutes occurred at 6:25 A.M., one-half hour later; and a third and final convulsion, three minutes in length, began at 7:10 A.M. There was no cry, no incontinence of urine or feces, and, as determined later from the patient, no preceding aura. The blood pressure was 162/104 at 8:30 A.M. and had risen to 174/120 by 10:45 A.M. There was a 3 plus albuminuria. The carbon dioxide combining power was determined to be 42 per cent, while the uric acid level was 4.2.

The patient remained semicomatose and disoriented throughout the next forty-eight hours, morphine being given only to control excessive restlessness.

Visualization of the eye grounds revealed no papilledema or hemorrhages, but some edema and exudate were noted, and the vessel ratio was reduced 1:3.

The Hanger cephalin flocculation test on March 30 was reported as 2 plus after 24 hours, 3 plus after 48 hours, thus indicating some liver damage.

The patient continued to improve rapidly thereafter. On April 1, the blood pressure was 140/90 and there was no albuminuria. The vulvar edema and that of the thighs had subsided. The patient was allowed out of bed on April 3. Her progress continued to be favorable, and she was discharged on April 12.

At the time of her discharge, her blood pressure was 124/76. The Hanger cephalin flocculation test was reported as equivocal after 24 hours, 1 plus after 48 hours. A Friedman test was reported as positive.

On the night of April 26, while at home, the patient developed a severe frontal headache associated with blurring of vision and marked vertigo. This was followed by several episodes of vomiting. Shortly thereafter, she developed severe epigastric pain, and the liver was palpable and tender. Blood pressure was 184/118. There was a 2 plus albuminuria. The clinical picture was that of an impending eclampsia, and the patient was given morphine for sedation.

By the following day, she was again symptom-free. No further treatment was given, and the patient had no further such attacks.

On May 29, the Friedman test was repeated and was negative. X-ray of the chest revealed no pleural or pulmonary pathology. The patient had no complaints except for a daily vaginal spotting, varying in color from a pinkish stain to a reddish-brown mucous discharge.

On June 21, pelvic examination revealed the cervix to be formed and closed with no evidence of erosion. The uterus was normal in size, regular in outline, and anterior. No adnexal masses were palpable.

On July 1, another Friedman test was reported as positive. The patient was reexamined ten days later, at which time she stated that the vaginal spotting had become more profuse and was bright red in color. The left ovary now seemed cystic and about twice normal size. The right ovary was slightly enlarged and cystic. Dilution Friedman tests were reported as strongly positive in the concentrated specimen and in the 1:1 dilution. Urine diluted 1:9 was negative in a third Friedman test.

In view of the cystic enlargement of the ovaries and the positive Friedman tests, even on dilution, chorionepithelioma of the uterus was considered; and the patient was again

hospitalized. Vaginal smears, taken according to the Papanicolaou technique, were reported by a qualified observer as negative for carcinoma. Pelvic examination was repeated on July 14, and the cystic enlargement of the ovaries seemed to have been progressive.

On July 15, 1947, preceding laparotomy, a dilatation and curettage were done. A minimal amount of normal appearing endometrium was obtained. At laparotomy, the uterus was slightly enlarged, somewhat softer than normal, and of a dark reddish-purple color. The previous hysterotomy was well healed, but a small area of bluish discoloration was noted at the upper angle of the scar. The tubes appeared normal. Both ovaries were the size of lemons, and contained numerous, thin-walled cysts filled with a clear yellow fluid. No enlargement of the pelvic or peri-aortic lymph glands was noted. The liver was palpated and seemed free of metastases. A total hysterectomy and bilateral salpingo-oophorectomy were performed.

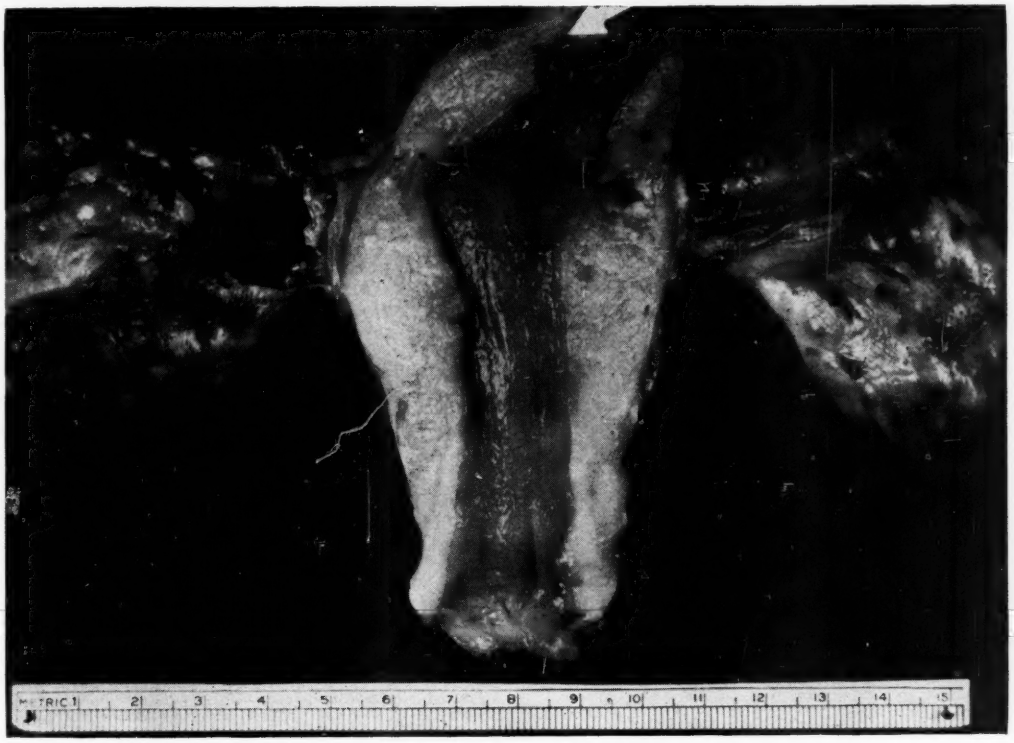

Fig. 1.—Photograph, showing uterus, both Fallopian tubes and ovaries. The uterus has been bisected, and arrow points to hemorrhagic nodule of chorionepithelioma in posterior wall.

On section of the uterus, the endometrial cavity measured 8 cm. in length and varied from 2 to 3.5 cm. in width. The endometrial surface was dark red and granular. The endometrium was less than 1 mm. in thickness. Projecting beneath the endometrium on the posterior wall of the fundus was an ovoid nodule, 0.5 by 0.7 cm., which was dark reddish-purple in color. Microscopic examination through this area was reported as follows:

"The hemorrhagic nodule is composed of groups of trophoblastic epithelial cells surrounding zones of extravasated erythrocytes and poorly defined, necrotic material. The units have a rim of polyhedral and irregular cells with ovoid and lobulated nuclei containing moderately coarse basophilic chromatin granules, and with clear cytoplasm. Granular acidophilic material is evident in some of the peripheral, but more conspicuously in the central portions of the aggregations. Shadows of trophoblastic epithelium can be recognized in some foci. Fibrillar and fibrous tissue surrounds the units, several of which show moderately

well-defined, hyalinized lamina propria. One small cellular aggregation is evident in an immediately adjacent portion of the myometrium. Dilated, thin-walled vascular channels are numerous in and adjacent to the hemorrhagic nodule. There is no additional evidence of further infiltration of the trophoblastic elements beyond the zone noted. The nodule is covered by compact, atrophic endometrium, showing fibrosis of the stroma.''

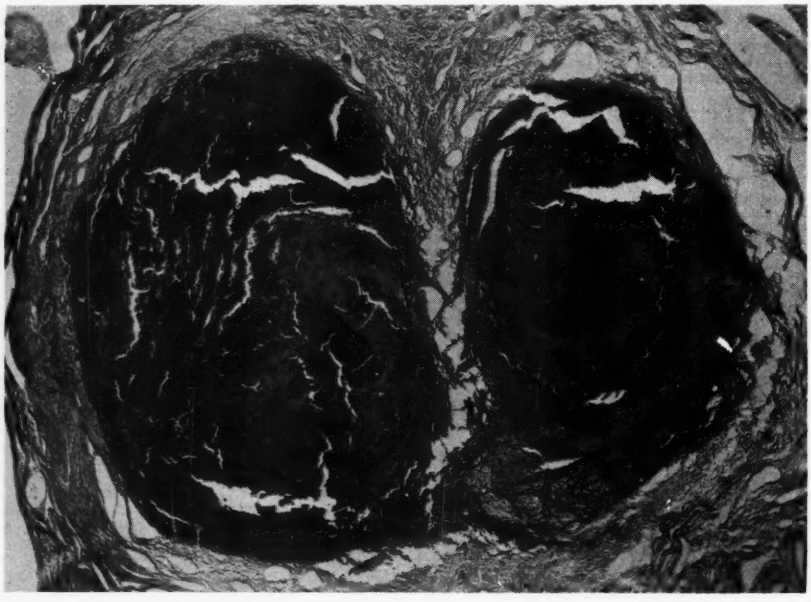

Fig. 2.—Photomicrograph (×30), showing nodule composed of two hemorrhagic areas, about which are grouped small islands of trophoblastic cells. The nodule is covered by compact, atrophic endometrium showing fibrosis of the stroma.

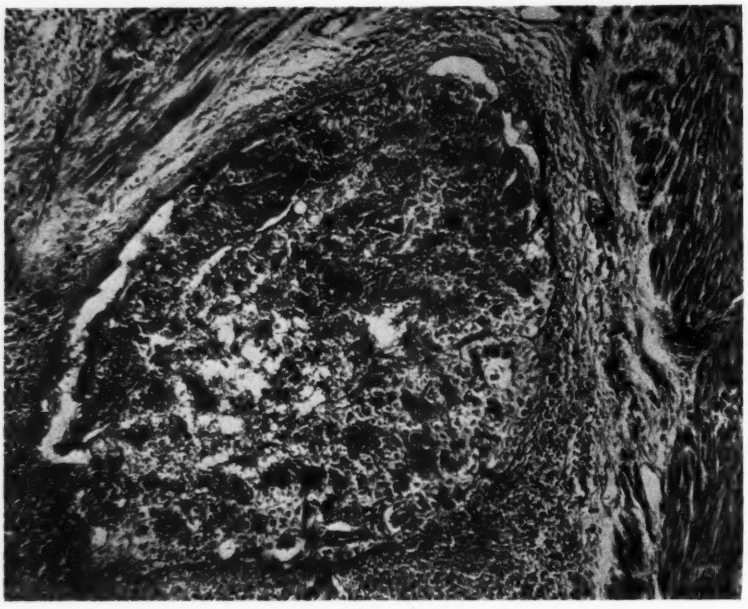

Fig. 3.—Photomicrograph (×125), showing unit of trophoblastic cells deep in myometrium.

The pathologic diagnosis was chorionepithelioma of the uterus. Histopathologic study of the ovaries revealed numerous lutein and follicular cysts.

Postoperative convalescence was uneventful. Roentgen studies of the skeletal system were made six weeks postoperatively, and they were entirely negative for any metastases. The Friedman reaction was still positive.

On August 23, a pea-sized nodule was palpated for the first time at the site of transfixation of the right round ligament to the vaginal vault. By September 6, this mass seemed almost to have doubled itself in size. Dilution Friedman tests were reported as positive for 1:1 dilution, negative for 1:9 dilution. In view of these, the patient was begun on a course of deep x-ray therapy. Roentgen therapy was completed on October 14, after a total of 2,000 r. to each of four pelvic ports had been given. The Friedman reaction with concentrated urine was negative. By November 13, the pelvic nodule had almost completely disappeared, and pelvic examination was entirely negative.

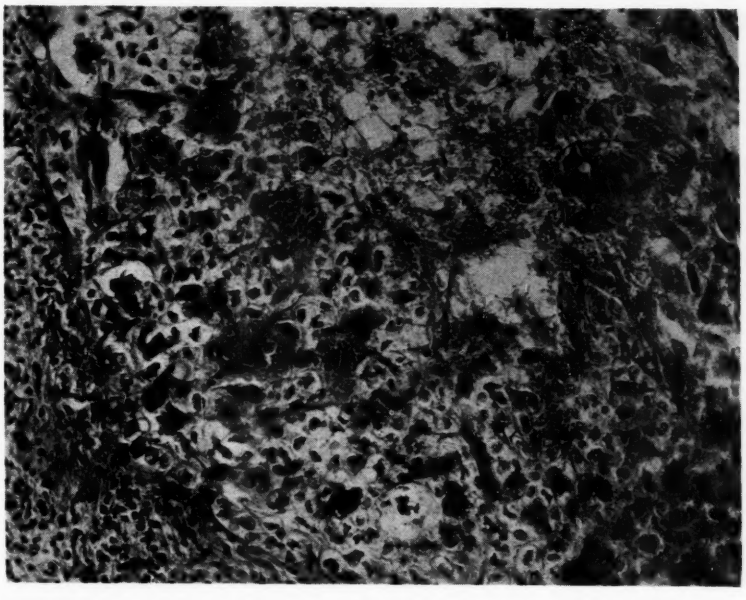

Fig. 4.—Photomicrograph (×250), showing cytology of trophoblastic island. The center of the aggregation is composed of granular, acidophilic material, among which shadows of trophoblastic epithelium are noted.

The patient has been followed at regular intervals since this time, and she has presented no unusual signs or symptoms. The Friedman tests have remained negative, and general and vaginal examinations have shown no evidence of recurrences or metastases.

Discussion

Hydatidiform mole occurs once in approximately 1,500 gestations. At Kings County Hospital, Brooklyn, in the ten-year period from 1937 through 1946, the authors found the incidence to be 1 in 1,349 pregnancies. This agrees closely with the incidence of 1 to 1,321 reported by Chesley et al.[1]

Mole is more frequent in multigravidas, and 40 per cent occur in women past the age of 40 years. Essen Moeller[2] states that chorionepithelioma has a greater incidence in this older group, and he recommends that all moles occurring in women past 40, and especially after 45, be treated by hysterectomy.

A fullness of the lower uterine segment with a bulging into the cul-de-sac seems to be an important sign peculiar to hydatidiform mole. This has been noted by us in three addi-

tional cases other than the one herewith reported, and H. Acosta-Sison[3] has already called attention to it as a diagnostic aid.

Anterior hysterotomy is recommended as the treatment of choice for hydatidiform mole when the uterus is enlarged beyond a twelve weeks' gestation. As pointed out by Hill,[4] (1) complete removal of the whole mole is possible under direct vision; (2) macroscopic evidence of invasion of the myometrium is available, allowing immediate hysterectomy if indicated; (3) accidental perforation of the uterus is eliminated; and (4) hemorrhage is controllable. Bland,[4] in 1928, reported two deaths from hemorrhage incurred by attempted evacuation of moles through the vaginal route.

The onset of eclamptic convulsions one week after evacuation of the mole was an unusual complication in the case presented. A diagnosis of postpartum eclampsia can only be made by exclusion in the presence of certain signs and symptoms, namely, (1) a history of pre-eclampsia or toxemia during the pregnancy; (2) an elevated blood pressure; (3) albuminuria; (4) edema; and (5) convulsive seizures. In the case reported, all these were present. The patient gave no history of epilepsy, and she has not exhibited any previous or succeeding convulsive attacks. The authors feel that this case represents a true postpartum eclampsia.

The incidence for chorionepithelioma developing subsequent to the treatment for hydatidiform mole is said to be between 2 and 3 per cent, although 50 per cent of patients with chorionepithelioma present a preceding history of hydatidiform mole.

Diagnosis of chorionepithelioma in the case above presented was made early in its onset, and treatment was radical despite minimal signs and symptoms. A reversal of the Friedman reaction after several months of negative results is, of course, highly important. However, a quantitative test positive in 1:1 dilution and negative in 1:9 dilution, suggests a reaction of unusually low titer. Such a rise in titer could be compatible with the development of a new pregnancy. But, and most significantly, a bilateral cystic enlargement of the ovaries was also noted; and observation of these, even over a period of several days, showed a rapid increase in their size.

The patient has continued to remain in good health postoperatively, and will be followed at regular intervals by clinical examination, roentgen studies, and Friedman tests.

The authors feel that the disease has been arrested in the patient by prompt and radical surgical intervention.

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MULTIPLE PREGNANCIES AT THE CHICAGO LYING-IN HOSPITAL, 1941 TO 1947

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IN NOVEMBER, 1941, Potter and Crunden[1] reported on 283 multiple pregnancies observed at the Chicago Lying-in Hospital between May 25, 1931, and Jan. 1, 1941. There were 281 sets of twins and 2 sets of triplets in this group. The present study covers an interval of six and one-half years, extending from Jan. 1, 1941, to July 1, 1947. During this period 22,943 women were delivered in this hospital. The deliveries included 257 multiple pregnancies, of which there were 252 sets of twins and five sets of triplets. This makes an incidence of 1:88.8 for multiple pregnancy, 1:91.0 for twins, and 1:4,588 for triplets. The incidence for twins born in the hospital in the previous series was also 1:91. The incidence of twins in both series is slightly lower than that of 1:87 which is given for the United States as a whole.

Parity.—In this series, 35.0 per cent (91) of the women with multiple pregnancies were primigravidas, 33.9 per cent (87) were in their second pregnancy, 14.5 per cent (37) in their third, 7.9 per cent (20) in their fourth, 2.0 per cent (5) in their fifth, 2.3 per cent (6) in their sixth and 2.8 per cent (7) in their seventh pregnancy. The remaining four women (1.6 per cent) had twins in their eighth, ninth, tenth, and eleventh pregnancies, respectively. In the entire group there were three women who had had previous sets of twins. Two of these had twins in their third and fourth pregnancies and the other produced twins in her seventh and ninth pregnancies. Forty-three per cent (9,924) of all the women delivered during this interval were primigravidas. The incidence of multiple births is only 1:109 in first pregnancies in comparison to 1:78 in subsequent pregnancies.

Birth Weight in Relation to Length of Gestation.—The data on gestational age and birth weight are based on 249 sets of twins, inasmuch as the menstrual age was not obtainable in three of the twin pregnancies. Seventy-seven and six-tenths per cent (193) of the women in this series delivered between the 240th and the 289th day, 4.4 per cent (11 cases) went past the 289th days and 18 per cent (45 cases) delivered before the 240th day, as calculated from the first day of the last menstrual period. Forty-three and eight-tenths per cent (109) of these mothers had their babies between the 265th and 295th day, within the period usually considered at term. The mean weight of infants born during this period was 2,737.7 Gm. The average difference in weight between the first and second twin was roughly 400 to 500 Gm. in the twins born between the 260th and 290th day. This difference was smaller in the groups of younger gestational age. The mean weights and average differences in weight between the twins for the various age groups are shown in Table I. As would be expected when compared with a group of 1,000 single pregnancies, the mean weights of twins born

at comparable periods of gestation is consistently lower (Table II). In most of the groups, the infants of a single pregnancy weighed between 500 Gm. and 600 Gm. more than an infant which was one of twins. In the groups at term this difference was 680 Gm.

TABLE I. DIFFERENCE IN WEIGHT IN THE TWO TWINS IN RELATION TO LENGTH OF GESTATION

LENGTH OF GESTATION FROM FIRST DAY OF LAST MENSTRUAL PERIOD	NUMBER OF CASES	PERCENTAGE OF CASES	MEAN WEIGHT	STANDARD OF DEVIATION	AVERAGE DIFFERENCE IN WEIGHT OF FIRST AND SECOND TWIN	STANDARD OF DEVIATION
Total pregnancies	249	100.	2,354.1	703.9		
Term (265-295 days)	109	43.8	2,737.7	479.6		
160-169	2	0.8	583.8	157.0	76.5	38.5
170-179	3	1.2	749.2	98.3	95.0	37.7
180-189	3	1.2	790.0	74.9	130.0	112.8
190-199	3	1.2	927.5	334.1	161.7	98.0
200-209	6	2.4	951.3	291.03	219.3	321.8
210-219	9	3.6	1,372.6	472.44	337.0	220.6
220-229	5	2.0	1,685.5	567.4	177.0	59.3
230-239	14	5.6	1,989.3	534.0	397.9	622.1
240-249	32	12.8	2,270.6	477.5	300.8	311.3
250-259	39	15.7	2,371.2	457.38	308.4	440.1
260-269	43	17.3	2,525.2	447.2	375.8	336.0
270-279	44	17.7	2,753.6	530.66	521.6	494.8
280-289	35	14.1	2,877.6	406.94	385.1	297.5
290-299	10	4.0	2,588.0	448.55	451.0	230.2
300-310	1	0.4	2,220.0	65.0	130.0	0

TABLE II. WEIGHT IN RELATION TO LENGTH OF GESTATION IN COMPARISON TO WEIGHT OF SINGLE INFANTS

LENGTH OF GESTATION FROM FIRST DAY OF LAST MENSTRUAL PERIOD	SINGLE PREGNANCIES 1,000 CASES		TWIN PREGNANCIES 249 CASES	
	PREGNANCY PER CENT	MEAN WEIGHT (GM.)	PREGNANCY PER CENT	MEAN WEIGHT (GM.)
Total pregnancies	100.	3.405.8	100.	2,354.1
Term (265-295 days)	77.55	3,418.3	43.8	2,737.7
160-169			0.8	583.8
170-179			1.2	749.2
180-189			1.2	790.0
190-199			1.2	927.5
200-209			2.4	951.3
210-219			3.6	1,372.6
220-229	0.7	2,716.6	2.0	1,685.5
230-239	0.6	2,050.0	5.6	1,989.3
240-249	1.92	2,923.6	12.8	2,270.6
250-259	2.43	3,133.3	15.7	2,371.2
260-269	9.5	3,098.9	17.3	2,525.2
270-279	27.4	3 325.0	17.7	2,753.6
280-289	31.85	3,591.0	14.1	2,877.6
290-299	19.21	3,618.6	4.0	2,588.0
300-309	4.15	3,650.0	.4	2,220.0
310-319	1.84	3,556.0		
320 plus	.40	3 777.0		

Length of Gestation.—The average length of gestation in 1,000 unselected single pregnancies reported by Potter and Crunden[1] was 281 days. In this series the mean length of gestation for 249 twin pregnancies was 256.7 days. In 63.5 per cent (158) of the cases, one or both infants weighed more than 2,500

Gm. and in this group the mean length of gestation was 269.4 days. The length of gestation is correlated with the combined weights of the babies in Table III. The correlation with weight groups is better when this method is used than when the larger infant determines the grouping. The mean gestational age for the 47.7 per cent of cases in which the infants had a combined weight over 5,000 Gm. was 271.2 days. The average gestational age for single infants weighing approximately 2,500 Gm. is about 267 days.

TABLE III. LENGTH OF GESTATION IN RELATION TO COMBINED WEIGHT OF TWINS*

COMBINED WEIGHTS OF INFANTS IN GM.	NO. OF CASES	PER CENT OF CASES	MEAN LENGTH OF GESTATION	STANDARD OF DEVIATION
Total pregnancies	254	100.0	256.2	27.32
Term (those with total weight over 5,000 Gm.)	121	47.7	271.2	13.80
500-999	2	.79	227.5	15.50
1,000-1,499	9	3.55	183.4	19.67
1,500-1,999	6	2.36	192.7	11.36
2,000-2,499	4	1.57	226.8	20.86
2,500-2,999	11	4.34	221.9	22.08
3,000-3,499	11	4.34	237.3	23.95
3,500-3,999	17	6.70	249.4	21.80
4,000-4,499	34	13.39	253.2	17.23
4,500-4,999	39	15.34	261.8	14.81
5,000-5,499	44	17.31	268.0	14.45
5,500-5,999	46	18.10	272.1	12.83
6,000-6,499	19	7.48	276.2	11.45
6,500-6,999	10	3.94	271.2	13.19
7,000-7,499	2	.79	275.0	4.00

*Table is based on 249 twin pregnancies and 5 triplet pregnancies.

Sex Ratio.—Two of the 252 sets of twins consisted of a full-term male infant plus a papyraceous twin whose sex was not determined. In the remaining 250 sets, the infants were of the same sex in 170 pairs and of the opposite sex in 80 pairs (female born first in 44, male born first in 36). Of the 170 pairs in which both infants were of the same sex, 85 pairs were boys and 85 pairs were girls. Thus, in 250 pairs of twins there were 250 boys and 250 girls. Most of these twins were born during the war years when popular legend tells us that more than the usual number of boys are born. In this series the ratio of females to males is higher than that of 100:105 given by the United States Bureau of Vital Statistics for total births in the United States. It is also considerably higher than the ratio of 100:117 for the earlier series of twins reported from the Chicago Lying-in Hospital.[1]

One of the five sets of triplets consisted of a full-term female infant plus papyraceous twins whose sex was not determined. There were two sets in which all the babies were females while the remaining two sets each consisted of two boys and a girl.

Placenta.—Of the 252 twin placentas, complete descriptions including the type of membranes and weight were available in 149. In 62 cases, a record of the type of placenta and membranes was present but the placenta was not weighed while in the remaining 41 cases no record of the placenta is available. The placenta was recorded as being double in 90 cases, single or fused in 121 cases, with no record in 41 cases. Of the 121 fused placentas, 73 were dichorionic and 48 were monochorionic. In the series of 90 double placentas, there were 52 sets of twins of the same sex and 38 sets in which the babies were of the opposite sex. The 73 fused dichorionic placentas were associated with 40 sets of twins in which the infants were of the same sex and 32 sets of twins of opposite sex. In this group there was one set in which the sex of one fetus, a papy-

raceous twin, was undetermined. Fused monochorionic twin placentas are ordinarily thought to indicate that the twins arose from a single ovum but in this series there were two sets of twins of different sexes in the group of 48 fused monochorionic placentas. There were no monoamniotic twin placentas, except for the twin papyraceous fetuses in the triplet pregnancy. The cords in this instance were extremely tangled and this was presumably responsible for fetal death.

Based on the 149 twin placentas for which complete information including weight is available, the average ratio between the weight of the placenta (without cord and membranes) and the combined birth weight of the twins was 1:6.7. This ratio is almost the same in the separate as in the fused placentas. In cases where the placentas were separate, the average ratio was 1:6.66 and in the fused group it was 1:6.72. This ratio, as in the first series of twins reported from this institution is slightly lower than the average for single pregnancies of 1:7.1 reported by Adair and Thelander.[2] In this series the ratios varied from 1:2.3 to 1:13.1. In general, the smaller babies were associated with proportionately larger placentas and vice versa. The largest set of twins in this series had a combined weight of 7,440 Gm. the placenta weighed 1,183 Gm. and the ratio was 1:6.3. It is obvious that there is a wide margin of safety in the amount of placental tissue necessary to provide adequate circulation for the infants.

The triplet placentas included one which was completely fused and four which consisted of two fused plus a single placenta. The (1) completely fused placenta was monochorionic and triamniotic; the fused placentas associated with the single placentas were (2) monochorionic and monoamniotic, (3) monochorionic and diamniotic, (4) dichorionic and diamniotic and (5) unrecorded. The infants in the five cases were (1) all female, (2) one female and two unknown, (3) and (4) one female and two males, and (5) all female. The average ratio of the weight of the placenta to the combined weight of the infants was 1:4.4.

Position.—In 44 per cent (111) of all cases, both babies were in a cephalic presentation. In 7.9 per cent (20), they were both breech. In 26.2 per cent (64), the first baby was cephalic and the second breech, while the reverse condition occurred in 13.19 per cent (33) of the cases. In 6.7 per cent (7) the second baby was in a transverse position and presented by the scapula or arm; 67.2 per cent (339) of the total of 504 babies were cephalic presentations and 28.3 per cent (143) were breech. Eighty-six second twins presented by the breech, in contrast to 57 first twins with a similar presentation. More first twins (194) had cephalic presentations than second twins (145). The frequency of the various presentations are shown in Table IV.

TABLE IV. POSITION OF TWINS AT DELIVERY

FIRST TWIN	SECOND TWIN	NUMBER OF CASES	PER CENT
Cephalic	Cephalic	111	44.1
Cephalic	Breech	66	26.2
Cephalic	Compound	13	5.1
Cephalic	Unrecorded	4	1.6
Breech	Breech	20	7.9
Breech	Cephalic	33	13.1
Breech	Compound	4	1.6
Compound	Cephalic	1	.4
Total		252	100.
Total infants with cephalic presentation		339	67.2
Total infants with breech presentation		143	28.3
Total infants with compound presentation		18	3.5
Total infants with no record		4	1.0
Total infants		504	100.

Fetal and Infant Mortality

Eighty-one of the 519 fetuses and infants resulting from 257 multiple pregnancies were stillborn or failed to survive the neonatal period (Table V). The eighty-one deaths include five abortions (under 400 Gm.), 29 stillbirths and 47 neonatal deaths. There were two sets of twins in which one fetus was listed as an abortion (under 400 Gm.), one set of triplets in which two were abortions (papyraceous twins), and one set of triplets in which one fetus was under 400 Gm.

TABLE V. MORTALITY IN RELATION TO WEIGHT

WEIGHT IN GM.	TOTAL BIRTHS	NEONATAL DEATHS	STILLBIRTHS	TOTAL NUMBER	MORTALITY PER CENT
2,500 and over	245 (1)*	2	2	4	1.6
2,000-2,499	146 (2)	5	5	10	6.8
1,500-1,999	51 (1)	3	3	6	11.8
1,000-1,499	34 (4)	16 (3)	3	19 (3)	55.9
400-999	38 (4)	21 (3)	16	37 (3)	97.4
Under 400	5 (3)		5 (3)	5 (3)	100.00
Total	519 (15)	47 (6)	34 (3)	81 (9)	15.6

*Triplets in parentheses.

The total uncorrected mortality for this series is 15.6 per cent. If the abortions and fetuses weighing less than 1,000 Gm. are excluded, the mortality is 8.2 per cent, and if those under 1,500 Gm. are excluded, it falls to 4.4 per cent. This latter figure is twice the total hospital mortality of 2.0 per cent which existed during the same period for infants and fetuses weighing over 1,500 Gm. Among those who weighed over 2,500 Gm., only 2 deaths and 2 stillbirths occurred. This is a rate of 1.6 per cent which is identical with that for single infants born during the same period. It is a common belief that a twin infant weighing under 2,500 Gm. is smaller than a single infant of equivalent gestational age and consequently is proportionately less premature and less handicapped than a single infant of equal size. These data seem to disprove that supposition, for twin infants weighing from 1,500 to 2,500 Gm. show over twice the mortality of single infants in the same weight groups; those weighing over 2,500 Gm. do not appear to be handicapped by the fact of being a twin.

Mortality in Triplets.—In only one set of triplets did all of the infants survive the neonatal period. These babies were all girls and weighed 2,360 Gm., 2,350 Gm., and 1,755 Gm. at birth. One set consisted of a full-term female infant weighing 3,190 Gm. and papyraceous twins which weighed 61 Gm. and 68 Gm., respectively. Another set, in which the weights were 470 Gm., 420 Gm., and 390 Gm., all died. None of the infants survived in an older set with weights of 1,160 Gm., 1,120 Gm., and 1,040 Gm. In the fifth set, the weights were 1,019 Gm., 885 Gm., and 920 Gm. The third baby in this group died during the neonatal period. The second one lived four months and the one weighing the most died at the age of five and one-half months. Of the fifteen babies included in five triplet pregnancies only six survived the neonatal period, and only four were alive at six months.

Mortality in Relation to Mode of Delivery.—(Table VI.) Of the infants in a cephalic presentation, 131 were delivered spontaneously, 119 by low or outlet forceps, 10 by midforceps, and two by high forceps. Of those with a breech presentation, 34 were delivered spontaneously, and 104 by extraction. Eighty-five infants were delivered by version and extraction (68 cephalic and 17 transverse) and 30 were delivered by the abdominal route. Considering only the stillbirths and neonatal deaths among infants weighing over 1,000 Gm., the

highest mortality (23.07 per cent) occurred in the spontaneous breech deliveries, while the next highest mortality (10.63 per cent) was in the group of breech extractions. It is interesting to note that the mortality in the group of spontaneous cephalic deliveries is 10.53 per cent and in a group almost as large delivered by low or outlet forceps the mortality was 4.2 per cent. This is due largely to the fact that forceps were rarely applied to the heads of the very small infants. Fortunately, there were no deaths in the twelve infants delivered by mid and high forceps. The infants delivered by version and extraction, all but one of whom were second twins, showed a mortality of 5.94 per cent for the group. The infant mortality for the cesarean section group (15 sections) was 3.57 per cent.

It has been suggested at times that the second twin is subjected to less hazard than the first because it passes through an already dilated birth canal; it has been thought by others to have a poorer chance of survival because of the possibility of placental detachment following the birth of the first twin. Among the 28 nonmalformed, nonmacerated fetuses and infants weighing over 1,000 Gm. who died or were stillborn, 15 were first born, 13 were second born. The difference is not significant.

TABLE VI. MORTALITY IN RELATION TO METHOD OF DELIVERY

METHOD OF DELIVERY	NUMBER OF BIRTHS		STILLBIRTHS AND NEONATAL DEATHS		
	FIRST TWIN	SECOND TWIN	WEIGHT UNDER 1,000 GM.	WEIGHT OVER 1,000 GM.	PER CENT MORTALITY OVER 1,000 GM.
Cephalic.—					
Spontaneous	89 (2)*	42 (2)	17 (1)	12	10.5
Low and outlet forceps	95	24	0	5	4.2
Mid forceps and high forceps	2	10	0	0	0
Version and extraction	1	84 (1)	1	5 (1)	5.9
Breech.—					
Spontaneous	24 (1)	10	8	6 (1)	23.1
Breech extraction	31 (2)	73 (5)	10 (3)	10 (1)	10.6
Cesarean section	15	15	2	1	3.6
No record	0	4 (2)	4 (2)	0	0
Total	257 (5)	262 (10)	42 (6)	39 (3)	8.1

*Triplets in parentheses.

Mortality in Relation to Cause of Death.—Table VII. All of the infants who failed to survive were subjected to postmortem examination except one in whom a clinical diagnosis of pneumonia was made. More than half of the infants (46) showed no abnormalities other than those associated with inadequate pulmonary function. Seven babies showed evidence of anoxia in the form of petechial hemorrhages of the lungs, heart, and thymus. Congenital anomalies were present in six. Three of these had multiple anomalies, one had a congenital muscular defect in the stomach which was responsible for rupture, one a spina bifida, and one a tracheo-esophageal fistula. In none of the cases did both twins exhibit anomalies One of the infants with multiple anomalies was a triplet. Pulmonary hemorrhage was found in six instances, pneumonia in four. Five babies of three twin pregnancies died of erythroblastosis. Both died after birth in one pregnancy, one died and one was stillborn in the second, and one died and one survived in the third. Another set of twins weighing less than 1,000 Gm. exhibited mild general edema but a diagnosis of erythroblastosis could not be made. Intracranial hemorrhage was demonstrated in only two instances.

Resorption atelectasis, with the formation of a hyaline membrane, was found twice. In two cases, perirenal hemorrhage was present; in one instance, it was associated with a hematoma of the liver.

TABLE VII. CAUSE OF DEATH IN RELATION TO WEIGHT

	STILLBIRTHS		DEATHS			
	1ST TWIN	2ND TWIN	1ST TWIN	2ND TWIN	TOTAL	
Over 2,500 Gm.—						
Anoxia	1			1	2	
Erythroblastosis	1			1	2	4
1,000 to 2,500 Gm.—						
No abnormalities	1	6	2 (1)*	4 (2)	13	
Anoxia	2	1	1	1	5	
Pulmonary hemorrhage			3	1	4	
Intracranial hemorrhage			1	1	2	
Erythroblastosis		1	2		3	
Pneumonia			2	2	4	
Malformations			3	1	4	35
Under 1,000 Gm.—						
No abnormalities	8	11 (3)	7	10	36	
Anoxia		1	1 (1)		2	
Pulmonary hemorrhage				1	1	
Hepatic hemorrhage				1 (1)	1	
Malformations		1		1 (1)	2	42
Total	13	21 (3)	22 (2)	25 (4)		81

*Triplets in parentheses.

Maternal Complications.—The belief that maternal complications are of increased frequency in multiple pregnancy is well borne out in this series. One hundred ten of the two hundred fifty-seven mothers had one or more complications during their pregnancies. Pre-eclampsia, the most common complication, was present in 39 cases, an incidence of 15.17 per cent, and an additional 5.84 per cent (15 cases) exhibited hypertensive toxemia in which an existing hypertension was aggravated by the pregnancy. Each of three women with pre-eclampsia and 1 with hypertension lost one infant; an additional mother with hypertension lost both infants. Four had one infant survive. This is a mortality rate of only 4.5 per cent for the 108 infants delivered by these women with pre-eclamptic or hypertension toxemia.

Anemia with a hemoglobin below 10 Gm. and contracted pelvis were each present in 13 cases. None of these mothers lost an infant.

Polyhydramnios occurred in 11 pregnancies and of all the maternal complications it seems to be the only one, other than placenta previa and abruptio placentae, that is associated with a significant increase in fetal mortality. Twelve fetal and neonatal deaths were associated with the eleven pregnancies which exhibited an abnormal increase in amniotic fluid. The high infant mortality associated with polyhydramnios is due mainly to prematurity. Nine of these fetuses and infants weighed less than 1,000 Gm., one weighed 1,300 Gm., one weighed 2,015 Gm. and had a spina bifida, and one weighed 2,375 Gm. and was badly macerated.

Premature detachment of the placenta occurred in four cases, placenta previa in three. Four fetal deaths were associated with premature placental detachment and two with placenta previa. Postpartum hemorrhage was found 26 times, an incidence of 10 per cent. The frequency is thought to be a result of poor contraction resulting from hyperdistention of the uterus.

Thirty of the 110 mothers had more than one complication, the most frequent combination being postpartum hemorrhage associated with either hyper-

tension or pre-eclampsia. Eclampsia did not occur in any of the cases. There was one maternal death in the series resulting from bacterial endocarditis with mitral stenosis and insufficiency, a maternal mortality of 0.39 per cent.

Cesarean sections were performed in fifteen cases. The maternal indications were as follows: previous section in six cases, pre-eclampsia two, placenta previa two, elderly primigravida with fibroids one (cesarean hysterectomy), elderly primigravida with hypertensive toxemia one, hypertensive toxemia with chronic renal disease one, essential hypertension one, and one case was sectioned after a twenty-two hour labor without progress.

Summary

In the six and one-half year period prior to July 1, 1947, there were 22,943 deliveries at the Chicago Lying-in Hospital. Among these there were 257 multiple pregnancies, an incidence of 1:91 for twins and 1:4,580 for triplets.

The mean birth weight in this series was 2,354 Gm.

The mean length of gestation for twin pregnancies was 256.7 days and for multiple pregnancies (including triplets) in which the combined weight of the babies was over 5,000 Gm. is 271.2 days.

The mortality for all infants and fetuses weighing more than 1,000 Gm. was 8.2 per cent and for those over 2,500 Gm. was 1.6 per cent. The mortality for single infants born in this hospital during the same period was 2.5 per cent over 1,000 Gm. and 1.6 per cent over 2,500 Gm.

The mean ratio between the weight of the placenta and the combined birth weight of the twins was 1:6.7, a ratio only slightly different from that of 1:7 found for single infants.

The twins associated with 48 monochorionic placentas were of the same sex in 46; of different sexes in 2. Those associated with dichorionic placentas were of the same sex in 92, of different sexes in 70.

The incidence of pre-eclamptic and hypertensive toxemia in this series was 21 per cent, in comparison to approximately 8 per cent for all deliveries. Postpartum hemorrhage and polyhydramnios also occurred more frequently than in single pregnancies.

Prematurity was the most important cause of death in this series of twin infants. Polyhydramnios, placenta previa, and abruptio placentae were the maternal complications most commonly associated with fetal mortality.

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THE EFFECTS OF VARIOUS ESTROGENIC PREPARATIONS

III. The Influence of Equivalent Amounts of Several Estrogens on the Vaginal Mucosa of Nonmenstruating Women

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IT IS the purpose of the present investigation to observe the effects of a *single* injection of a variety of estrogenic preparations, and to compare them with each other. Emphasis has been placed upon three features which can be measured objectively by a study of the vaginal smear: (1) the "lagtime," i.e., the number of hours between injection of the hormone and the appearance of changes in the vaginal secretion indicative of an estrogenic response; (2) the degree of stimulation; and (3) its duration. Concomitantly, attention has been given to changes in subjective symptomatology in all patients except those who were postmenopausal women entirely free of climacteric symptoms.

Methods and Procedure

Forty-one women, ranging from 24 to 78 years of age, were subjects of the study. Of these, fourteen were postmenopausal, sixteen, surgical castrates, and nine, menopausal. Of the two remaining subjects, one had had a unilateral oophorectomy and hysterectomy, and the other, at 46 years of age was menstruating regularly but had complaints characteristic of the menopausal syndrome. The group classified as "menopausal" included those women whose menses had ceased within the preceding 3 years and whose symptomatology was distinctly climacteric.

Several of the subjects received injections of two preparations so that a total of 57 studies was made. In all instances in which patients received more than one preparation, an interval of not less than three weeks was allowed to elapse between administration of the two doses. In this way, any "priming" effect of the first injection upon the vaginal mucous membrane was minimized.

The estrogenic preparations* included estradiol as a solution in sesame oil and propylene glycol and as a suspension in water; estradiol dipropionate in sesame oil; estradiol benzoate in peanut oil and in propylene glycol; and estrone in aqueous suspension. Estradiol, in free and esterified form, was administered in 1 mg. doses and estrone in 4 mg. doses, as previous studies had indicated a weight-for-weight activity ratio of that degree.[1, 2]

In each case, vaginal smears were taken daily for an average of one week prior to the administration of estrogen. From a study of these each patient was classified as to smear type according to the criteria of Papanicolaou and Schorr,[3] when these applied. Changes subsequent to therapy were evaluated in the light of these initial observations. Following injection of the hormone, daily smears

*All estrogenic preparations used in these studies were furnished by Dr. Edward L. Henderson of the Schering Corporation, whose courtesy is herewith gratefully acknowledged.

were taken in each instance for an average period of 10 days (240 hours). Approximately 900 vaginal smears have been studied. Details related to the technique of taking the smears, the staining method and the daily tabulation of observations have been described previously.[1]

Results

Eight women received injections of estradiol dipropionate in sesame oil, four of estradiol benzoate in peanut oil and three of estradiol benzoate in propylene glycol. Estradiol in aqueous suspension was administered to sixteen subjects, estradiol in sesame oil to three, and estradiol in propylene glycol to two. Estrone in aqueous suspension was employed in 20 instances (Tables I and II).

Thirty-two of the 57 injections of estrogen were followed by a follicular response in the vaginal epithelium which was undoubtedly due to the hormone administered. In addition, seven tests, in four women, produced questionable results. These included Cases 3A and 18A, women exhibiting cyclic ovarian activity prior to the study; Case 1A, in whom one test dose of hormone produced cytological alterations in the vaginal epithelium not sufficiently definitive for classification; and Case 14A, in whom previous therapy had apparently resulted in "priming" of the vaginal mucosa. These four cases have been previously reported and will be given no further consideration here.[2] In eighteen instances, the vaginal smears were not altered by the injection of the estrogen. Among these were five patients who had received estradiol dipropionate in sesame oil; two, estradiol benzoate in propylene glycol; one, estradiol in sesame oil; three, estradiol in aqueous suspension; and seven, estrone in aqueous suspension.

1. *Lag-Time.*—The lag-time varied from 48 to 168 hours (Table II). Had we accepted the earliest evidence of a change in the vaginal smear as indicative of estrogenic activity, this period might have been somewhat shortened. However, some false positive reactions would also have been reported. It seemed best to adhere strictly to the grading of the degree of response from 1 plus to 4 plus according to the criteria noted in the footnote to Table I. In the average patient, four to five days were usually required to elicit such a quantitative reaction. This lag-period was not dependent on the type of estrogen administered. Of the five subjects tested with an estrogen in propylene glycol, three showed a response in the vaginal smear with an average lag-time that was slightly longer than that noted following the use of an estrogen in oil or water. Similar results have been obtained in connection with a larger series of patients in whom greater amounts of estrogen were administered in the corresponding media,[1]

2. *Duration of Estrogenic Effect.*—The over-all variation in the duration of the estrogenic response ranged from 24 to 192 hours (Tables I and II). It

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*Status: PM — Postmenopausal
M — Menses have ceased within a three-year period
SC — Surgical Castrate
SO — Single oophorectomy and hysterectomy
Me — Menstruating
Numbers in parentheses denote number of years since cessation of menses.

Rx: A — 1 mg. estradiol dipropionate in sesame oil
B — 1 mg. estradiol benzoate in peanut oil
C — 1 mg. estradiol benzoate in propylene glycol
D — 1 mg. estradiol in sesame oil
E — 1 mg. estradiol in propylene glycol
F — 1 mg. estrone in aqueous suspension
G — 1 mg. estradiol in aqueous suspension

Degree: CCT = change in cell type
+ = 10 — 25% cornification
++ = 25 — 50% cornification
+++ = 50 — 75% cornification
++++ = 75% and over of cornified cells present

TABLE I. DATA FROM 41 NONMENSTRUATING WOMEN RECEIVING A SINGLE INJECTION OF AN ESTROGEN

				RESPONSE				
NO.	AGE	STATUS*	SMEAR TYPE	R*	LAGTIME (HOURS)	DURATION (HOURS)	DEGREE*	OBSERVATION PERIOD (HOURS)
1	52	PM (6)	Pseudoleucopenic	A	–	–	–	132
2	55	PM (7)	Intermediate	A	–	–	–	132
3	70	PM (30)	Atrophic	A	–	–	–	132
4	78	PM (29)	Atrophic	A	–	–	–	132
11	43	SC (9)	Atrophic	A	–	–	–	168
53	49	SC (3)	Intermediate	A	102	30	+	144
54	49	M	Mucous	A	102	111	++	219
55	46	M	Premenstrual	A	60	159	++++	219
19	68	PM	Pseudoleucopenic	B	48	?	+++	60
47	62	PM	Pseudoleucopenic	B	102	138	+	264
48	66	PM	Pseudoleucopenic	B	102	78	++	264
49	60	PM	Atrophic	B	108	30	+	264
57	52	PM (5)	Mucous	C	120	24	+	264
60	54	PM (6)	Pseudoleucopenic	C	–	–	–	264
63	61	PM (9)	Mucous	C	–	–	–	264
50	49	SC (11)	Pseudoleucopenic	D	120	24	+	219
51	53	M	Premenstrual	D	–	–	–	144
52	47	M	Premenstrual	D	96	48	++	144
59	54	PM (6)	Pseudoleucopenic	E	108	132	+	264
65	58	PM (12)	Premenstrual	E	120	108	+	264
1a	54	M	Intermediate	F	–	–	CCT	188
2a	41	SC (2)	Mucous	F	–	–	–	292
3a	46	Me	Cyclic	F	?	?	?	264
4a	61	PM (28)	Premenstrual	F	96	72	+	264
5a	24	SC (2)	Premenstrual	F	48	192	+++	264
6a	48	M	Pseudoleucopenic	F	–	–	–	264
8a	41	SC (2)	Premenstrual	F	96	96	++	264
10a	42	SC (6)	Premenstrual	F	–	–	–	144
11a	52	SC (22)	Premenstrual	F	120	148	+++	264
12a	52	M	Premenstrual	F	168	84	++	264
				F	96	120	+	240
13a	48	M	Premenstrual	F	–	–	–	264
14a	52	M	Intermediate	F	?	?	+++	216
15a	28	SC (1)	Premenstrual	F	–	–	–	264
16a	33	SC (6)	Intermediate	F	96	152	+++	336
18a	37	SC	Cyclic	F	?	?	?	264
19a	28	SC (4)	Premenstrual	F	120	72	+	336
20a	53	SC (7)	Pseudoleucopenic	F	72	96	++	264
21a	41	SC (18)	Premenstrual	F	–	–	–	264
22a	46	SC (3)	Intermediate	F	96	72	++	264
23a	50	SC (12)	Intermediate	F	–	–	–	264
1a				G	–	–	–	264
2a				G	72	96	++	192
3a				G	?	?	?	240
4a				G	120	72	+	264
6a				G	96	144	+++	264
8a				G	120	48	++	264
9a	45	SC (10)	Atrophic	G	48	154	++	288
11a				G	72	144	+++	264
12a				G	120	48	+	240
14a				G	–	–	CCT	240
15a				G	–	–	–	216
16a				G	72	168	++++	264
18a				G	?	?	?	264
19a				G	–	–	–	336
21a				G	48	120	++	264
23a				G	144	48	+	264

(For footnote to Table I see opposite page.)

TABLE II. CHARACTERISTICS OF THE VAGINAL RESPONSE OF NONMENSTRUATING WOMEN TO SINGLE DOSES OF ESTROGENIC PREPARATIONS*

NUMBER OF SUBJECTS					LAG-TIME (HOURS)		DURATION (HOURS)	
TOTAL	REACTING	DRUG	MENSTRUUM	DOSE (MG.)	RANGE	AVERAGE	RANGE	AVERAGE
8	3	Estradiol dipropionate	Sesame oil	1	60-102	88	30-159	100
4	4	Estradiol benzoate	Peanut oil	1	102-108	90	30-138	82
3	1	Estradiol benzoate	Propylene glycol	1	120		24	
3	2	Estradiol	Sesame oil	1	96-120	108	24-48	36
2	2	Estradiol	Propylene glycol	1	108-120	114	108-132	120
21	10	Estrone	Aqueous suspension	4	48-168	100	72-192	110
16	10	Estradiol	Aqueous suspension	1	48-120	90	48-168	109

*Questionable responses are not included in this table.

was longest on the average in the case of free estradiol adminstered in a menstruum of propylene glycol (120 hours). With this exception, all preparations in watery suspension produced a more prolonged effect than the solutions in oil or propylene glycol. This may be attributed to the fact that the hormone in situ is not in a soluble state. However, the individual variations were considerable and do not warrant any far-reaching conclusion. The condition of the subject at the time of injection undoubtedly played no little role in the pattern of the response elicited.

3. *The Degree of Vaginal Response.*—Inspection of the individual case records (Table I) shows that, in almost every instance, the degree of the follicular reaction attained can be directly correlated with its duration. Neither duration nor degree of stimulation can be closely related to the type of estrogen administered in the *individual* case.

4. *A Comparison of the Effects of Estrone and Estradiol in Aqueous Suspension.*—To each of fifteen subjects, either estrone or estradiol was administered in aqueous suspension. Not less than three weeks later, after the vaginal smear showed a reversal to the pretreatment status, the second estrogen was given and vaginal changes again observed.

As previously mentioned (Table I), the changes in the vaginal mucosa were of such a nature that their relationship to the administration of the estrogen could be questioned in Cases 3a, 14a, and 18a (Table III).

In some instances, one estrogen was employed first, in others, the second. The order of their usage appeared to make little difference in the results obtained. For instance, four women, who first received estrone, failed to react objectively, whereas the subsequent injection of estradiol was followed by a follicular response in the vaginal smears. This might suggest that the primary injection of hormone had a "priming" effect, not necessarily apparent in the vaginal epithelium, and that the second injection produced noticeable changes because it acted upon an already partially receptive membrane. However, in one case, No. 19A, estrone, the first injection, caused a follicular reaction while, following subsequent treatment with estradiol, the smears showed no alterations in cytological features. Similarly, in Case 1A, estrone produced transient changes in the vaginal epithelium and a later injection of estradiol brought about no response. One cannot, therefore, attach too much significance in this series of experiments to the order in which the preparations were employed.

TABLE III. A COMPARISON OF THE EFFECTS OF ESTRONE AND ESTRADIOL IN EQUIVALENT DOSES UPON THE APPEARANCE, DURATION, AND HEIGHT OF THE VAGINAL RESPONSES OF 15 NONMENSTRUATING WOMEN

CASE NO.	AGE (YEARS)	THE VAGINAL RESPONSE					
		LAG-TIME (HOURS)		DURATION (HOURS)		DEGREE*	
		ESTRONE	ESTRADIOL	ESTRONE	ESTRADIOL	ESTRONE	ESTRADIOL
1a	54	–	–	–	–	CCT	–
2a	41	–	72	–	96	–	++
3a	46	?	?	?	?	?	?
4a	61	96	120	72	72	+	+
6a	48	–	96	–	144	–	+++
8a	41	96	120	120	48	++	++
11a	52	120	72	148	144	+++	+++
12a	52	168	120	84	48	++	+
14a	52	?	–	?	–	+++	CCT
15a	28	–	–	–	–	–	–
16a	33	96	72	152	168	+++	++++
18a	37	?	?	?	?	?	?
19a	28	120	–	72	–	+	–
21a	41	–	148	–	120	–	++
23a	50	–	144	–	48	–	+
Average	44	116	96	108	99	++	++

*See footnote Table I.

Five women first injected with estrone, responded to both preparations. Two reacted more rapidly to estrone than to estradiol and 3 responded more promptly to estradiol than to estrone. In one instance, the duration of the changes in the vaginal smear was the same for each of the two injections, in three cases, it was longer following injection of estrone, and, in one instance, it was greater after the administration of estradiol. The degree of the response elicited by each of the two preparations was the same for three subjects. Estrone produced a greater amount of cornification of the vaginal epithelium than estradiol in one woman and the action of estradiol was more pronounced than that of estrone in one individual.

Symptomatic Relief in Relation to Alterations in the Vaginal Smear.—Most of the patients suffering from climacteric disturbances were among the groups of women who were tested with estrone and estradiol, respectively, in aqueous suspensions. The ability of estrogen to relieve symptoms without altering the vaginal smear has already been discussed at length in relation to the subjects of the present study.[2] Several points may be emphasized here. Symptomatic relief occurred prior to the appearance of the alterations observed in the vaginal mucosa, but the rapidity and degree of response were not quantitatively related to the changes later observed in the vaginal smears. In a number of instances, improvement in the general condition was acknowledged by the patient when objective changes were absent. The duration of symptomatic relief following administration of 1 mg. estradiol or an equivalent dose of estrone varied from three to ten days.

Summary

1. Forty-one women were treated with one or more injections of equivalent amounts of seven estrogenic preparations to a total of 57 tests. In thirty-nine tests, changes occurred in the vaginal mucosa; of these, however, seven were difficult to evaluate in relation to the administration of the estrogen. No objective response followed any of the remaining eighteen injections.

2. Free estrone, free estradiol, and the benzoic acid and dipropionic acid esters of the latter were the estrogens employed in these tests. Estrone was given

in doses of 4 mg. and each estradiol preparation in amounts of 1 mg. per injection. Estrone was used as an equeous suspension only. Free estradiol was similarly employed, and also as a solution in propylene glycol and sesame oil, respectively. Estradiol dipropionate was prepared as a solution in sesame oil only; the benzoate was administered in menstrua of peanut oil and propylene glycol, respectively.

3. Daily vaginal smears were taken for a control period of approximately one week prior to therapy and for an average period of ten days thereafter. Approximately 900 smears were studied.

4. The average lag-time (hours between injection and vaginal response) for each preparation was as follows: estradiol dipropionate in sesame oil, 88; estradiol benzoate in peanut oil, 90; estradiol in aqueous suspension, 90; estrone in aqueous suspension, 100; estradiol in sesame oil, 108; estradiol in propylene glycol, 114; and estradiol benzoate in propylene glycol (one case), 120.

5. The average duration in hours of the vaginal response initiated by estradiol dipropionate in sesame oil was 100; by estradiol benzoate in peanut oil, 82; by estradiol in sesame oil, 36; by estradiol in propylene glycol, 120; by estradiol in aqueous suspension, 109; and by estrone in aqueous suspension, 110.

6. The degree of follicular activity varied widely with the preparation used and from subject to subject, but in any given instance, was directly proportional to the duration of the vaginal changes.

7. Climacteric patients reported symptomatic relief starting one to three days following injection and persisting for from three to ten days thereafter.

Conclusions

About four to five days after the injection of 1.0 mg. estradiol, free or esterified, or its equivalent, 4.0 mg. estrone, regardless of menstruum, alterations in the vaginal secretion appear in the majority of nonmenstruating women. Under the conditions of our experiments, the time elapsed between the injection and the appearance of a change in the vaginal smear (lag-time) was approximately the same for each of the seven preparations employed.

The duration of the estrogenic response varied widely. The preparations producing the longest periods of follicular activity were estradiol in propylene glycol and in aqueous suspension and estrone in aqueous suspension.

The degree of stimulation of the vaginal mucosa varied considerably from subject to subject. The duration and degree of estrogenic response were directly correlated in any given individual but neither bore any demonstrable relationship to the specific preparation used.

The majority of climacteric patients reported symptomatic improvement, starting, on an average, one to three days after injection of the hormone and persisting for from three to ten days. The degree of relief of symptoms cannot be correlated with the objective findings in the vaginal mucous membrane.

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MYOMAS DURING AND AFTER THE MENOPAUSE

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THE patient past the childbearing period who is found to have myomas of the uterus has long presented a problem. In 1891, J. T. Johnson,[1] of Washington, D. C., reported to the Southern Surgical and Gynecological Association that the "rule" stated in the textbooks—that uterine myomas cease to grow after the menopause—has many more exceptions than was generally supposed at the time. He recommended more frequent and earlier resort to radical operation in the treatment of these tumors in menopausal women. In the years since 1891, the continued growth of myomas after cessation of the menses, and the occurrence of cellular changes, such as benign degeneration and malignant change, have been so frequently associated, that there is at the present time considerable doubt that myomas ever increase in size after the menopause by simple growth. Whether his assumption concerning growth was right or wrong, Johnson did call attention to the fact that myomas can and do produce symptoms after the menopause.

The decision as to whether or not asymptomatic myomas should be left alone and watched, and as to how radical the treatment should be in the face of minor symptoms, is one to be made after consideration of the features of each individual case, and with a background of a knowledge of the behavior of these tumors during and after the menopause.

With a view to increasing this background of knowledge, a study was undertaken at the University Hospitals of Cleveland of all the hospital patients over 45 years of age having myomas of the uterus, in a five-year period from Jan. 1, 1942, through Dec. 31, 1946. Of these, the patients whose myomas were removed were studied in detail with regard to symptoms, preoperative diagnosis, the pathologic changes found, age, parity, menstrual history, and marital status.

Table I shows that there were 1,990 women with diagnosed myomas admitted to the hospital in the given five-year period. Of these, 617, or almost one third, were in or past the menopausal age group, and 408 (66.01 per cent) of them had hysterectomies performed because of their myomas.

In Table II, those 408 patients with which this report is concerned are broken down into the natural divisions of those who have definitely stopped menstruating, using three months or more of continuous amenorrhea as the criterion, and those who are still in the menopause. Approximately one fourth of the patients were postmenopausal. Each of these groups is then divided into patients on whom major surgery was performed for no other reason than a preoperative diagnosis of myomas, and those who had additional reasons for opera-

tion. This distinction is made very definite, and the statistics presented in the latter part of this report are taken from those patients who had surgery done for no other indication than the myomas. It is the practice in most clinics today, and rightfully so, I believe, to remove a myomatous uterus when major pelvic or vaginal surgery is undertaken for some other reason, even though the tumors are asymptomatic and might well be left undisturbed. Patients who had indications for surgery other than myomas will include many whose tumors were not causing, and would never have caused, trouble. There is a total, then, of 201 patients over 45 years of age who were operated upon solely because of uterine myomas.

TABLE I. MYOMAS AT UNIVERSITY HOSPITALS, CLEVELAND. JANUARY, 1942, THROUGH DECEMBER, 1946

Total patients of any age with myomas	1990
Patients over 45 years old with myomas	617
Patients over 45 treated by hysterectomy	408

TABLE II. DISTRIBUTION OF PATIENTS ACCORDING TO MENOPAUSE AND INDICATION FOR OPERATION

After the menopause	117 (28.7 per cent)		
Myomas the only reason for operation			42
Additional reasons for operation		75	
During the menopause	291 (71.3 per cent)		
Myomas the only reason for operation			159
Additional reasons for operation		132	
Totals	408	207	201

The fact that nonparous uteri are more likely to develop myomas than parous uteri is well known. On the basis of this, one would expect a higher proportion of the patients in this series to be nulliparous, than occurs in an unselected group of women of similar age, and such is the case, as is shown in Table III. Te Linde[3] quotes Hinselmann to the effect that approximately 20 per cent of women over 35 are nulliparous. Of the 408 patients studied here, 33.1 per cent were nulliparous, 29.8 per cent of those whose symptoms occurred during the menopause, and 41.1 per cent of those who had trouble after the menopause. In other words, one third of these patients were nulliparous, whereas only one fifth of the women over 45 in the general population have never had children.

The racial distribution of patients as determined in this series has little general significance. The proportion of Negro patients in this study is only about half of the proportion of that race in the University Hospitals of Cleveland's total census. A possible explanation for this may be the fact that myomas occur at an earlier average age in Negro women and grow to a larger size than they do in white women, and are therefore more frequently removed during the childbearing period.

The marital state of the patients studied agrees quite closely with that of the general population. Hinselmann[3] estimated that about 10 per cent of women over 35 have not been married, and these figures of 8.9 per cent and 11.1 per cent average to about 10 per cent.

On the basis of a series of 408 patients, then, we can conclude that marital status has no influence on the incidence of symptomatic myomas of the uterus after the age of 45, and that parity influences the development of symptoms indicating radical surgery only as it influences the incidence of myomas in general.

TABLE III. DISTRIBUTION OF PATIENTS ACCORDING TO PARITY, COLOR, AND MARITAL STATUS

	TOTAL	PAROUS	NULLIP.	COLORED	WHITE	MARRIED	SINGLE
During menopause	291	204 70.2%	87 29.8%	33 11.4%	258 88.6%	265 91.1%	26 8.9%
After menopause	117	69 58.9%	48 41.1%	28 24%	89 76%	104 88.9%	13 11.1%

The rest of this discussion is based entirely on those 201 patients who had no other indication for operation than myomas of the uterus. In other words, the tumors in these patients were considered by the surgeon to be causing enough symptoms or to be dangerous enough in themselves to warrant hysterectomy.

In gathering and calculating the statistics on this subject, there were two obvious factors that characteristically played a part in determining the decision to operate. As would be expected, these were size of the tumor, and the symptoms complained of by the patient. Of course, other factors are important, such as general health of the patient and mental attitude, but size and symptoms were the only two that could be compared statistically. In addition, there is a third factor, which did not lend itself to statistical comparison in this series, but which is equally important in the decision in favor of radical surgery. This is the increasing size of a tumor after the cessation of the menses.

Table IV shows the weight of the uterus and tumor from patients during and after the menopause. Roessle and Roulet[4] give the average weight of the normal uterus after the age of 45 as 50 Gm., with variations of 25 Gm. in either direction. Since preoperative estimation of the size and weight of the uterus and tumor must be based on palpation, it has been determined from the measurements and weights of surgical specimens that a uterus increased to the size of a 2½ months' pregnancy by myomas will weigh 450 to 500 Gm. The average size, then, of these 201 tumors was about the size of a two and one-half to three months' pregnancy. A few were within the normal limits of weight, but, as will be seen later, these uteri were the ones that had some other condition, undiagnosed preoperatively, which probably was causing the symptoms that led to operation.

TABLE IV. WEIGHT OF UTERUS AND TUMOR WHEN MYOMAS WERE THE ONLY REASON FOR OPERATION

	DURING MENOPAUSE	AFTER MENOPAUSE
Average weight	456 Gm.	542 Gm.
Extreme weights	75 and 2,890 Gm.	30 and 2,870 Gm.
Normal uterus	50 Gm.	50 Gm.

The most common symptom, as might be expected, was bleeding. A few of the patients presented two complaints that were considered equally important, so each was listed as an individual symptom in Table V. Those patients who are still menstruating present a particularly difficult problem in the evaluation of irregular bleeding. Many women have erratic periods and menorrhagia, and even metrorrhagia, during the last year or two of their menstruating life, without any pathologic change in the uterus. To say that a small or medium sized myoma that happens to be present at this time of life is the cause of the irregular bleeding, is an unjustified statement. It is difficult to imagine how subserous myomas or small intramural tumors can cause bleeding. Submucous nodules or larger intramural masses, and particularly pedunculated submucous tumors, do cause bleeding by alteration of the endometrial circulation, by necrosis and ulceration of the tumor mass, and perhaps by simple increase in the total amount of functioning endometrium, in the case of the very large myomas which in-

crease the size of the uterine cavity. The problem of why these tumors cause bleeding is still certainly far from solved, and the physiology of it presents an interesting challenge.

TABLE V. CHIEF SYMPTOMS WHEN MYOMAS WERE THE ONLY REASON FOR OPERATION

	BEFORE MENOPAUSE	AFTER MENOPAUSE
Bleeding	102	13
Pain	30	9
Growing mass	28	10
Backache	15	1
Urinary	5	2

The problem facing the clinician, however, is not why myomas cause bleeding but—are they causing the bleeding in the particular patient he is treating? Some light is thrown on this question by a comparison of the size of the tumor and the findings of the pathologist in the bleeding cases of this series. As shown in Table VI, one-fourth of the patients who were still menstruating showed, in addition to the myomas, other changes that could well account for the bleeding, and almost two-thirds of the postmenopausal patients showed such changes. Although this latter group is very small, and the figure of 61.5 per cent is not statistically important for this reason, I believe the proportion is so large that it has definite significance. Table VII shows the relative frequency of those associated conditions that could have been causing the bleeding, and it will be noted that they are all common to this period of life, and are all known to be the cause of uterine bleeding.

TABLE VI. DISTRIBUTION OF BLEEDING PATIENTS ACCORDING TO PATHOLOGIC EXPLANATION FOR BLEEDING

During Menopause.—	
Total patients	102
Patients with only myomas to explain bleeding	77 (75.5 per cent)
Patients with findings in addition to myomas to explain the bleeding	25 (24.5 per cent)
After menopause.—	
Total patients	13
Patients with only myomas to explain bleeding	5 (38.5 per cent)
Patients with findings in addition to myomas to explain the bleeding	8 (61.5 per cent)

TABLE VII. PATHOLOGIC FINDINGS OTHER THAN MYOMAS TO EXPLAIN BLEEDING

	DURING MENOPAUSE	AFTER MENOPAUSE
Endometrial polyp	12	4
Cervical polyp	5	
Atypical hyperplasia	4	2
Carcinoma of cervix	2	
Carcinoma of fundus	1	2
Chronic endometritis	1	
	25	8

All were undiagnosed before hysterectomy.

The most interesting and probably the most instructive point brought out by this study is made by comparing the weight of the specimens with the pathologic findings, as is done in Table VIII. In women during the menopause whose uteri presented only myomas as an explanation for the bleeding, the average weight of the uterus and tumors was 501 Gm., whereas in those organs which also had polyps, atypical hyperplasia, or carcinoma to account for the bleeding, the average weight was only 288 Gm. A difference even more marked is

seen after the menopause, where the respective weights were 643 and 227 Gm. In other words, small myomas are not likely to be the cause of bleeding, and when small myomas are found in the bleeding menopausal or postmenopausal patient, the surgeon is not justified in blaming the tumors, until he has eliminated such more likely possibilities as cervical and endometrial polyps, atypical hyperplasia of the endometrium, and fundal or cervical carcinoma. To put the figures differently for the patients past the menopause, of all the postmenopausal patients studied whose uteri weighed less than 500 Gm. (or were smaller than a three months' pregnancy), two-thirds of them had conditions other than the myomas to explain the bleeding.

TABLE VIII. WEIGHT OF UTERUS AND TUMOR CORRELATED WITH PATHOLOGIC FINDINGS IN BLEEDING PATIENTS

	DURING MENOPAUSE	AFTER MENOPAUSE
Myomas the only explanation for bleeding	501 Gm.	643 Gm.
Additional explanations present	288 Gm.	227 Gm.

Now, undoubtedly, some of these patients were best treated by hysterectomy, but it would seem that many of them would have been cured by a simple polypectomy or thorough curettage, and spared a laparotomy.

The one other symptom worthy of discussion is increasing size of a uterine tumor after the menopause. There were five patients in the postmenopausal group who presented this complaint. The myomas of each of these patients showed marked hyaline degeneration. In addition, edema was found in three, and cystic degeneration, focal hemorrhages, and calcification were each found in one of the tumors. There was no evidence of malignant change in any of them. All but one of the specimens weighed over 500 Gm., and the one that weighed less was noted to be increasing in size only by a physician.

When presented with an increasing tumor after the menopause, the physician naturally is concerned about malignant change. Frank,[5] in his textbook, makes a definite statement to the effect that myomas can not only continue to grow after the menopause, but may begin to develop after cessation of the menses, and quotes six different authors to support the statement. He does not clarify the word grow, but it is assumed that he means a natural growth, and not an increase in size due to an abnormal process. On the other hand, many recent texts maintain that myomas do not grow after the menopause except to increase in size because of degenerative processes or malignant change. Whichever statement is correct, the phenomenon of simple growth in uterine myomas after the menopause is at least rare, if it does occur, and any detectable increase in size warrants hysterectomy, on the probability that degenerative processes or malignant changes have been taking place. Of the five leiomyosarcomas of the uterus encountered in this series, all occurred before the cessation of regular menstruation. Four definitely originated in myomas, and the fifth was so extensive that the origin could not be determined. Only one of the specimens weighed less than 450 Gm.

There were seventeen patients, not included in this series, whose myomas were treated with radium or x-ray during the same five-year period. All but two were white private patients, and their ages ranged from 46 to 60 years. All but one had abnormal bleeding as their chief complaint, and the size of the myomas varied from one and one-half to four times that of a normal uterus. Eight patients had an associated atypical hyperplasia of the endometrium, which was considered an additional indication for the use of radiation therapy. Adequate follow-up information on these seventeen patients was not obtained in this study, but it is of interest to note that, in this same five-year period,

hysterectomy was performed because of myomas on five patients who had received deep x-ray therapy for myomas from one to twenty years previously.

Before concluding, it would be pertinent to determine what proportion of women over the age of 45 who have myomas of the uterus develop symptoms indicating surgical removal of the tumors. It is almost impossible to determine this accurately, but a rough approximation can be obtained. Crossen and Crossen[2] quote Kolb as having found that 50 per cent of all women over 50 have uterine myomas. On the basis of this and the approximately 20,000 admissions of women over 45 years old to University Hospitals of Cleveland during the five-year period studied, we can estimate that about 10,000 menopausal and postmenopausal women having myomatous uteri made up the field from which came the 408 patients studied in this series. In other words, approximately 4 out of 100 myomas cause serious trouble during or after the menopause.

Summary and Conclusions

Four hundred eight women over 45 years of age with myomas of the uterus surgically removed were studied, with special attention to symptoms, size of tumor, and pathologic changes found. The marital status of the patient had no significance, and parity was significant only as it influenced the incidence of fibroids in general. Bleeding was the most common symptom, but only in the larger myomas (those above the size of a 2½ to 3 months' pregnancy) could the bleeding be consistently attributed to the tumors. With one-fourth to two-thirds of the smaller myomas, other causes for the bleeding were present, which were not diagnosed preoperatively. This is taken to indicate too hasty a decision in favor of hysterectomy and incomplete preoperative studies. Of the patients who noted increasing size of the tumor, all five had benign degenerative changes in the myomas, but no malignant changes were found.

In this series, approximately four out of 100 myomas in the general hospital population were troublesome enough to be considered an indication for hysterectomy. The average size of the tumors removed was about that of a 2½ to 3 months' pregnancy. It is believed that the above incidence of hysterectomies can be appreciably reduced by performance of thorough curettage before the final decision for hysterectomy is made in the instance of myomas smaller than a 2½ months' pregnancy, particularly in patients with bleeding as the chief symptom.

From the foregoing statistics and discussion, it is concluded that women approaching or in the menopause, who are found to have asymptomatic myomas smaller than a 2 months' pregnancy, may be carefully watched and given reasonable assurance that their tumors will probably not cause any trouble. The myomas larger than a 3 months' pregnancy are potentially troublesome, and, if the patient's general health and mental attitude are favorable, hysterectomy is indicated.

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STUDIES ON SURVIVING HUMAN PLACENTAL TISSUE

I. A Search for Pressor and Antidiuretic Factors

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THE placenta has long been favored as the culprit in hypotheses as to the cause of eclampsia. The most cogent evidence for this belief is the fact that hydatidiform mole, in the absence of a fetus, carries a high incidence of preeclampsia, and occasionally is accompanied by eclampsia. This association is particularly striking since the toxemia in molar pregnancy occurs at about the beginning of the second trimester, while, in pregnancies with fetuses, toxemia is rare before the third trimester.

At about the turn of the century, placental extracts, press juices, and autolysates were extensively investigated for the "elusive eclamptic toxin." Such preparations, given intravenously to animals, frequently caused convulsions and prompt death. For the most part, however, they were inactive when injected by other routes. Further investigation has shown that these immediate effects were usually either nonspecific anaphylactoid reactions, or were attributable to particulate blocking of the lung capillaries (Lichtenstein[8]). Oden,[11] Obata,[10] Dieckmann,[5] and more recently Schneider[17] have given intravenous injections of placental extracts presumably free of particulate matter, and produced quick death. According to Schneider,[17] this may depend upon intravascular clotting caused by placental thromboplastin.

Dixon and Taylor,[6] in 1908, reported that they had obtained a powerful pressor action in their placental extracts. However, the following year Rosenheim,[16] working in their laboratory, showed that the pressor activity was attributable to parahydroxyphenylethylamine and other bases formed by the action of putrefactive bacteria which had contaminated their preparations. Sterile placental extracts were without pressor activity.

More subtle factors than direct pressor agents have been sought in recent years. Dexter and Weiss,[3] after failure to find a pressor substance, could demonstrate no renin or reninlike enzymes in placental tissue. Page[13] could find no 1-dopa decarboxylase activity in placentas from normal or eclamptic pregnancies.

Many studies have been made of the histologic pathology, especially of the liver, following injections of placental preparations. These will be reviewed in a later paper, but it appears that no one using placental derivatives has produced a liver lesion generally accepted as reproducing the picture often, though not always, seen in human eclampsia, viz., fibrin thrombosis with focal peripheral hemorrhagic necrosis. Dieckmann[4] did obtain such a lesion in dogs by feeding meat in conjunction with the intraportal injection of "tissue fibrinogen" (thromboplastin). Since the placenta is rich in thromboplastin, this experiment may be significant.

Opinion is divided as to whether patients with toxemia excrete more antidiuretic substance in the urine than do normal individuals with comparable

degrees of oliguria caused by dehydration. However, Ham and Landis[7] have reported that the urine and placentas of toxic patients do contain an antidiuretic substance which can be differentiated from the pituitary hormone.

In spite of all the negative and conflicting results, many writers still hold the hypothesis that pressor amines or "split proteins" are produced in ischemic areas of the placenta, and that these are the causative agents in eclampsia. Page[12] has marshalled a number of clinical observations consonant with the placental ischemia hypothesis. Relative ischemia of the placenta might be correlated with the increased incidence of toxemia seen in primiparous pregnancies, molar pregnancies, multiple pregnancies, polyhydramnios, placental infarction, cases of abnormal placentation, and in the hypothyroid, hypopituitary types of patients. It might also be related to intrapartum eclampsia and the rising frequency of toxemia as pregnancy approaches term.

We have taken up the general problem, utilizing a method which has vast possibilities in many fields. Lindbergh[9] has devised a perfusion apparatus in which one may keep organs or portions of organs alive for weeks. The conditions of the perfusion, oxygen supply, food supply, etc., may be varied at will. Here, then, is a means of experimental attack upon the question as to whether placental tissue produces the eclamptic toxin. This is a new approach, since the methods of extraction and autolysis remove either preformed substances or degradation products. Here we have an opportunity to investigate the production of substances by surviving or, if we elect, by dying placental tissue.

In the present paper, we shall describe a series of experiments in which we have extended the range of the so-far fruitless quest.

Methods

Since absolute sterility is essential in the culture of organs, we have used only placentas from patients who were sectioned with unruptured membranes. An artery on the fetal side was cannulated, and glucosol was forced in by hand bulb, thus washing out the blood from the tissue supplied by the cannulated artery. A piece of washed-out tissue, weighing from 6 to 20 Gm. was then isolated and any "bleeders" were tied off. It was usually possible to take an entire cotyledon, which is an anatomical unit in that it is supplied by one artery and drained by one vein. The tissue was then put into the organ chamber of the pump, and the apparatus sealed and thoroughly "gassed" with a mixture of 80 per cent oxygen, 15 per cent nitrogen, and 5 per cent carbon dioxide. Perfusion was begun within an hour of the time that the placenta had been removed from the uterus. The initial perfusion medium was 300 ml. of 15 per cent human serum in Tyrode solution. At three-day intervals (usually), the tissue was changed to another pump and a fresh lot of perfusion medium used. Details of the variations will be indicated in reporting the results. All perfusions were done with a pressure of 96/54 mm. Hg in the organ. The pulsation rate was 90 per minute. The temperature of the system was 37° to 38°. In general, we adhered faithfully to the details of technique as outlined by Carrel and Lindbergh.[1]

In looking for a pressor substance in the perfusates, we used cats anesthetized with intraperitoneal sodium pentobarbital. A carotid artery was cannulated, and the blood pressure recorded on a smoked drum, using a mercury manometer. The perfusates, their concentrates, derivatives, etc., were injected into the femoral vein.

The assay for antidiuretic substance was carried out much as described by Teel and Reid,[15] using three to six rats for the assay of each preparation. The rats were gavaged with 0.2 per cent sodium chloride solution in quantities

equivalent to 5 per cent of the body weights. When diuresis was well established, about 80 minutes later, a second gavage equal to three per cent of the body weight was given, and 1 ml. of the placental perfusate was injected subcutaneously. The urine output of each rat was then determined over a three-hour period. The three-hour output was calculated in terms of percentage of the water load (load=sum of gavages plus 1 ml. of injected perfusate minus urine volume output during the establishment of diuresis).

In the experiments to be reported here, the placental perfusates, and their controls, were concentrated ten times in a vacuum desiccator at room temperature. The controls were portions of the perfusion media which had been withheld when the experiments were started.

The urinary chlorides were determined by the method of Volhard and Harvey.[14]

Results

Survival of the Tissue.—In all, more than 75 successful placental cultures have been made. Pieces of placenta have been kept in good condition for as long as four weeks. At the end of the experiments, the tissue looked normal grossly and histologically, and was still producing gonadotrophic hormone. The tissues perfused throughout with only 15 per cent serum showed nuclei which did not stain with normal intensity. During some of the experiments, the tissue had withstood periods of anoxia with no apparent damage. Near the end of some experiments, undiluted plasma from the blood bank was used. The tissues seemed to oxidize citrate rapidly, as evidenced by considerable rises in the pH of the perfusate (citrate ion oxidized, leaving sodium to combine with water and carbon dioxide to form sodium bicarbonate).

Failure to Find Pressor Activity.—The only effect ever found upon the blood pressure, following intravenous injection of the perfusates or their derivatives, was an occasional drop. Usually and characteristically the blood pressure remained constant within 10 mm. Hg.

The general plan of procedure was to perfuse the placental tissue for three days under the conditions described above. The placenta was then transferred to another pump and perfused for three or four days anoxically. The gas phase in this variation was 95 per cent nitrogen and 5 per cent carbon dioxide. Following the anoxic perfusion, the placenta was again transferred to another pump with fresh medium, and again perfused in oxygen. After three days, another variation was tried. Total periods of perfusion ranged from 11 to 28 days. Some experiments were done in which the perfusion rate was greatly reduced, and the tissue was presumably dying; here, the period of perfusion was 24 hours.

In the first experiments, the original perfusates were assayed; the volume of injection was from 20 to 50 ml. Since these elicited no pressor responses, the whole volume of perfusate (250 to 275 ml. recovered from the pump) was concentrated ten times in a vacuum desiccator at room temperature. Twenty ml. of the concentrate, or 2/3 of the entire volume of perfusate, failed to elicit any pressor response. The anoxic perfusates never increased the blood pressure, and in about one third of the cases caused rather marked drops in pressure.

In the first three experiments, the perfusion medium consisted of 15 per cent serum and 85 per cent Tyrode solution. Since so dilute a serum might not contain enough of a hypothetical precursor for the placenta to make a pressor substance, later experiments were made with varying concentrations of serum or citrated plasma. The maximal serum concentration used was 70 per cent, and the maximal plasma concentration was "undiluted" bank plasma (which actually is about 80 per cent plasma and 20 per cent citrate and dextrose solu-

tion). None of the perfusates gave pressor responses. These perfusates were concentrated from two to ten times, depending upon the protein content.

Two experiments were done in which the perfusate was dialyzed for 24 hours against two changes of distilled water. In one, the unconcentrated perfusate was dialyzed, and in the other dialysis was done after concentration. Both the residual and the dialysate were then concentrated and assayed separately. No pressor response was found.

In another experiment, a branch of the cannulated artery was tied off, thus "infarcting" about one-half of the placental tissue. No pressor substance was found in the perfusate, nor could any be extracted from the dead portion.

All perfusates had their controls in perfusion medium saved from the lot put into the pump. The control media were concentrated, or dialyzed, incubated, etc., simultaneously with the test perfusates. All solutions were adjusted to pH 7.3 to 7.5 with carbon dioxide, before injection.

In sum, we have not been able to find a condition under which surviving placental tissue produces a detectable amount of a pressor substance. There are, of course, many variables which have not been tried, or even thought of—but that is the difficulty with negative results.

TABLE I. THE EFFECT OF PLACENTAL PERFUSATES UPON DIURESIS IN RATS*

CONDITIONS OF PERFUSION	CONTROLS			TEST		
	NO. OF RATS	PERCENTAGE OF WATER LOAD EXCRETED IN 3 HOURS		NO. OF RATS	PERCENTAGE OF WATER LOAD EXCRETED IN 3 HOURS	
		MEAN	RANGE		MEAN	RANGE
Rapid, 3 days	3	54.4	54-55	3	53.9	45-59
Rapid, 6 days	6	48.2	36-62	6	55.1	41-80
Rapid, 4 days	4	54.9	51-59	4	29.4	12-51
Rapid, 4 days	6	41.2	30-48	6	40.1	20-76
Rapid, 3 days	5	54.0	40-80	6	45.0	16-79
Slow, 1 day	4	44.5	25-65	6	29.3	19-40
Slow, 1 day	3	55.2	35-81	5	25.3	0-56
Slow, 2 days	6	38.2	26-53	5	31.7	16-41
Slow, 2 days	6	54.7	43-73	6	22.8	1-41
Slow, 2 days	5	72.0	57-83	5	55.5	44-71

*All placentas from normal patients. All perfusions done in 80 per cent oxygen. All perfusates concentrated ten times in a vacuum desiccater at room temperature.

Antidiuresis.—About half of the placental perfusates assayed have shown an antidiuretic effect when concentrated ten times and injected subcutaneously into rats. With one exception, the active perfusates have come from experiments in which the placenta was purposely perfused very slowly, i. e., under conditions of artificial "ischemia." Also, with one exception, the assayed perfusates of all placentas so perfused have shown antidiuretic activity. We do not have enough experiments to determine whether this slow perfusion is the controlling factor. The results of all experiments are shown in Table I, and in Fig. 1. The findings in all rats injected with the "ischemic" perfusates are depicted in Fig. 2. The spread of the distribution curves, as in most bio-assays, is most distressing to one who likes to base conclusions on clear-cut differences. However, 63 per cent of the test rats excreted less than 40 per cent of the water load, while only 17 per cent of the animals injected with the control concentrate failed to excrete more than 40 per cent of the load.

Chloruresis.—Whether the pituitary antidiuretic hormone has a chloruretic effect is still *sub judice*, although most workers have thought that it has. Ham and Landis[7] have shown that the urinary excretion of chlorides increases steadily as the dose of Pituitrin is increased over a 1,000 fold range. They state that

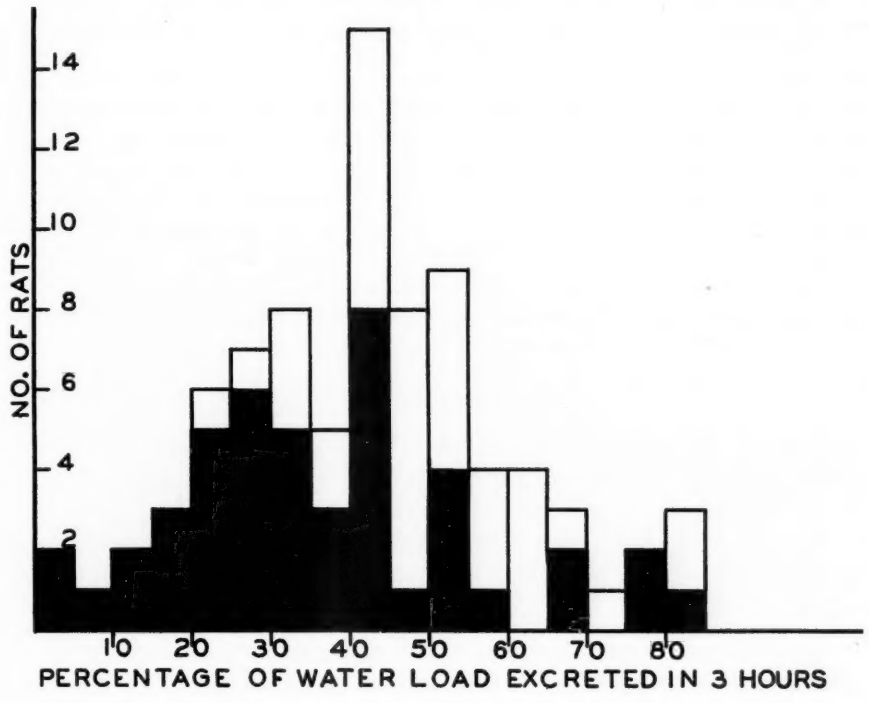

Fig. 1.—Diuresis in individual rats, as percentage excretion of the water load in three hours.

□ Control
■ Test

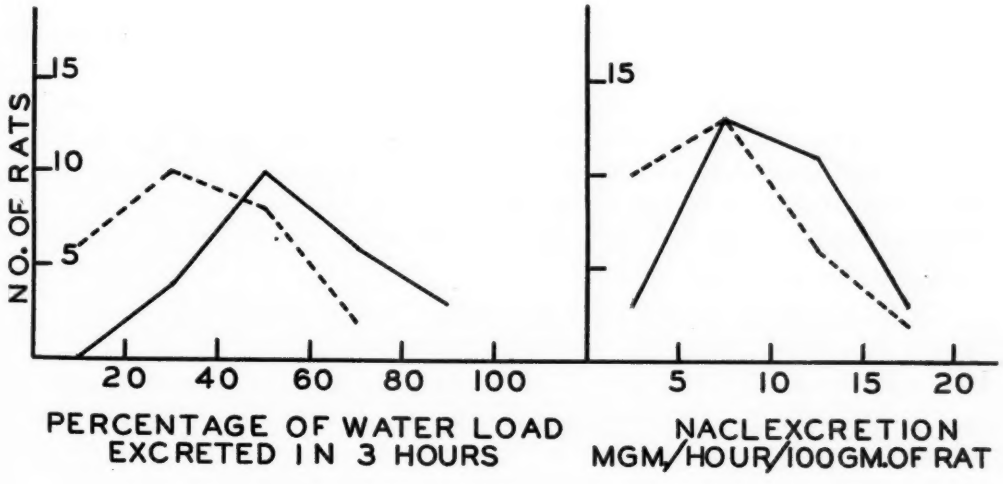

Fig. 2. Fig. 3.

Fig. 2.—Frequency distributions of diuretic response in rats injected with perfusates from "ischemic" perfusions (broken line), and their controls (unbroken line).

Fig. 3.—Frequency distributions of chloride excretion in the rats represented in Fig. 2.

Unbroken line: Control.

Broken line: Test.

this is in agreement with a prediction made by Silvette that Pituitrin might be assayed more accurately by its chloruretic effect than by its antidiuretic activity. Several other workers, however, have attributed the chloruresis to the Pitocin contaminating the Pituitrin preparations. According to Smith,[18] the Pitocin effect may be referable to changes in the rate of glomerular filtration rather than to a specific effect upon the renal tubular reabsorption.

Since some of our perfusates seemed to be definitely antidiuretic, we have determined the chloride excretion in the same experiments. As Fig. 3 shows, no chloruretic effect was ever observed. There was no increase in either the total excretion or the urinary concentration of chloride in any experiment. This, perhaps, accords with the finding of Ham and Landis[7] that there is no chloruretic activity associated with the antidiuretic substance extracted from placentas of patients with toxemia of pregnancy.

Discussion

Our assays for a pressor substance have obviously been acute experiments. They have ruled out the presence of a direct pressor agent in our perfusates, and thus speak against the hypotheses built around the production of pressor amines in the placenta. We have not determined whether these placental perfusates can cause hypertension secondarily and through the intermediation of some other agent.

In view of the negative results in the search for a pressor activity in our perfusates, the question rises as to whether we used enough placental tissue. A rough calculation seems to indicate that we did. The average weight of placental tissue perfused was about 15 Gm. The volume of concentrated perfusate injected in the pressor assays represented two thirds of the total perfusate, and would therefore be equivalent to the three-day metabolite production of 10 Gm. of placenta. The assays were made with cats weighing about 2 kg. In proportion, this would be equivalent to 300 Gm. of placenta producing metabolites for three days in a 60 kg. woman.

The experiments do not rule out the possibility that the placenta does produce a pressor substance. We have perfused the fetal vessels, and it is conceivable that substances of high molecular weight might not pass from the maternal constituent of the placenta into the fetal circulation. Clinically, pre-eclampsia usually does not occur in the fetus of the toxic mother; the baby's blood pressure is normal.[3]

It is interesting that antidiuretic activity in the placental perfusates was usually associated with slow "ischemic" perfusion of the tissue. Ham and Landis[7] found an antidiuretic activity in the extracts of placentas from patients with toxemia, but not from normal patients. No conclusion can be drawn as to the relation between these two observations, but it is worth pointing out that our placental perfusion experiments were undertaken on the hypothesis that inadequate perfusion might imitate what happens in the placenta of a patient developing toxemia.

In a review of the literature, Chesley[2] concluded that the cause of edema formation in incipient pre-eclampsia is unknown, since none of the physical factors studied could be incriminated as the primary cause. It is possible that

the placental antidiuretic substance plays a role in the accumulation of water in these toxic patients, but we cannot assess its importance. Edema is not pre-eclampsia.

Summary and Conclusions

Human placental cotyledons were kept alive in Lindbergh pumps and perfused under varying conditions of oxygen supply, perfusion rate, protein content of medium, etc.

None of the perfusates showed any pressor activity.

Perfusates from placentas artificially "ischemic" usually had some antidiuretic activity, while those from placentas perfused more adequately usually had no such activity.

The antidiuretic perfusates had no effect upon the urinary excretion of chlorides.

We wish to acknowledge our indebtedness to Herbert S. Gasser, Edric B. Smith, and John Campo of the Rockefeller Institute, for the loan of the Lindbergh-Carrel apparatus.

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CLINICAL EVALUATION OF SULFAMERAZINE IN POSTPARTAL AND POSTABORTAL SEPSIS*

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THE purpose of this paper is to report the results of treatment of eighty-eight cases of postpartal and postabortal sepsis using sulfamerazine.

Sulfamerazine, the monomethyl derivative of sulfadiazine, is 2-sulfanilamide-4-methylpyrimidine, and was synthesized at about the same time as sulfadiazine by Roblin and his coworkers[1, 2] and by Sprague and his associates.[3] Preliminary studies[1, 2, 3] indicated that this derivative had promising chemotherapeutic activity, but it received little attention until recently when attempts were made to find a more satisfactory sulfonamide.

Pharmacological and clinical studies of sulfamerazine administered orally,[4-13] have shown that a higher concentration in the blood is attained more rapidly and maintained longer than that attained by equal doses of the more commonly used sulfonamides. These characteristics result from its rapid and more complete absorption from the gastrointestinal tract, and its slower excretion by the kidneys. Careful clinical and experimental investigations have been made on the solubility, absorption, excretion, and toxicity of sulfamerazine.

Welch, Mattis, Latven, Benson, and Shiels[13] showed that more sulfadiazine than sulfamerazine was excreted in the urine in the first twenty-four hours despite the fact that the blood reaching the kidney was much lower in its sulfadiazine content. They then anticipated that with equivalent blood concentrations of the two drugs, with a slower renal excretion of sulfamerazine, a definitely lower concentration of that drug should occur in the urine at any given time. This, plus the greater solubility of the free and acetylated forms of sulfamerazine in neutral or acid urine, in comparison with the sulfadiazine, offers additional protection to the urinary tract from crystallization. Others[4, 6, 7, 10, 11, 14, 15, 16, 17] have found sulfamerazine to be more soluble in acid urine than sulfadiazine and hence more desirable from the standpoint of less renal toxicity.

Various workers[4, 6, 7, 9, 11, 13, 14] have demonstrated in both experimental animals and man that higher blood levels are obtained more rapidly and maintained longer with sulfamerazine than with the more commonly used sulfonamides. Likewise, it has been observed that this drug is removed from the blood stream more slowly than similar preparations. Sulfamerazine also produces a higher concentration in the blood with a smaller dose than sulfadiazine.[4, 6, 10, 11, 12, 13] Thus, less frequent doses of the drug are necessary to maintain an adequate blood concentration.[9, 10, 11, 13] The rapidity of absorption suggests that intravenous injection may not be necessary when it is desired to produce an adequate blood concentration quickly.[4, 6, 13]

*The sulfamerazine used in this study and funds for this study were supplied by Sharp & Dohme, Inc.

Extensive work has been done on the relative toxicity of sulfamerazine. Some of these observations were from the clinical use of the drug in treatment of various infections,[4, 5, 6, 8, 9, 10, 12, 15, 18] and others were the direct results of laboratory experiments on animals.[13, 14] In general, the observers concluded that sulfamerazine showed a low incidence of toxic manifestations. It was no more toxic than the commonly used sulfonamides[4, 5, 6, 9, 10, 12, 13, 19] and probably more desirable in so far as solubility and renal toxicity were concerned.[14] Sulfamerazine has further been studied with respect to its antibacterial activity. Experimental observations[1, 2, 20, 21] on various animals and in vitro have shown sulfamerazine to be quite effective in the treatment of pneumococcal septicemia, meningitis, staphylococcal and streptococcal infections. The drug has been used clinically with good results in the treatment of pneumococcal pneumonia, meningococcal meningitis, erysipelas, streptococcic infections, gonococcal urethritis, nonspecific urinary tract infections, and colon bacillus infections.[5, 6, 8, 9, 10, 12, 15, 18] The general conclusions are that in the majority of cases sulfamerazine is equally as effective a therapeutic agent as sulfadiazine.

Present Study

The present study was conducted on postpartal and postabortal septic cases on the Tulane Obstetrics and Gynecology Service at Charity Hospital of Louisiana at New Orleans. The majority of the cases consisted of postpartal patients who were considered septic if they had a temperature of 100.4° F. for two consecutive days. However, in a few there was gross evidence of infection on admission and chemotherapy was started immediately. Likewise, a few cases were treated prophylactically because of low-grade fever and a foul lochia post partum.

Of the eighty-eight patients followed who were treated with sulfamerazine, there were sixty-seven cases of postpartal endometritis; four of acute endometritis from septic incomplete abortions; three of puerperal morbidity, cause undetermined; two of endometritis and parametritis; three of postpartal pyelitis; three of pyelitis and endometritis; one of postpartal sepsis following intrapartum sepsis from prolonged rupture of the membranes; one septic criminal abortion with pelvic thrombophlebitis and pulmonary infarction; one of endometritis and suppurative thrombophlebitis of the pelvic veins; one of endometritis from an incomplete septic abortion with retained placenta; one of endometritis from prolonged ruptured membranes with thrombophlebitis of the superficial internal saphenous vein; and one of pelvic thrombophlebitis.

At the beginning of this study, the initial dosage of sulfamerazine was 1 Gm. orally, followed by 0.5 Gm. every four hours, day and night, with an equal dose of sodium bicarbonate or potassium citrate. Later the dosage was changed to an initial dose of 3 Gm. orally and 1 Gm. every six hours, day and night, with equal doses of sodium bicarbonate or potassium citrate. Toward the last of the series the sodium bicarbonate or potassium citrate was discontinued altogether. With the smaller dosage of sulfamerazine, blood samples were taken about midway between the second and third dose of the drug, and with the larger dosage a blood sample was obtained three hours after the initial dose. Using the method of Bratton and Marshall,[22] the concentration of free sulfamerazine in whole blood was determined on the sample obtained and then every twenty-four hours for the first two days and every other day thereafter. A record was kept of the temperature at the time of drawing the blood sample, the highest temperature reading of the day, and the daily intake and output. Blood cultures were taken on all cases prior to administration of the drug.

Combined penicillin and sulfamerazine therapy was used in thirteen of the eighty-eight cases. These were patients who were either very septic on admission or whose septic course did not respond readily to sulfamerazine therapy

alone. Two of the eighty-eight cases did not respond to sulfamerazine after five days and continued to run a low-grade fever, but did become afebrile when sulfadiazine was substituted.

The majority of the blood cultures were reported negative but there were eight cases of *Staphylococcus albus,* one of *Staphylococcus aureus pyogens,* and three of *Staphylococcus albus hemolyticus* reported. However, in view of the clinical course of the corresponding patients, these positive cultures are believed to be the result of contamination. Likewise, urinary findings were essentially negative on the majority of cases reported, unless a pyelitis was associated with the endometritis. Gram-negative bacilli were the usual offending organism in such cases.

The total dosage of sulfamerazine varied from 6.5 Gm. given over a two-day period in a case of postpartal endometritis to 40 Gm. given over an eleven-day period to a patient with a septic abortion with pelvic thrombophlebitis and pulmonary infarction. However, in the majority of cases, the average total dose of the drug was about 12 to 16 Gm. given over a three- to four-day period. The concentration of free sulfamerazine in the blood, obtained as previously described, varied markedly in eleven patients treated with 1 Gm. initially and 0.5 Gm. every four hours, from a low level of 0.92 mg./100 c.c. on a sample obtained two hours after the second dose of the drug to a high of 12.4 mg./100 c.c. on the fourth day of treatment. The average blood concentration was about 5 mg./100 c.c. in the majority of cases. In the remainder of the cases, giving 3 Gm. of the drug as the initial dose and 1 Gm. every six hours, the blood concentrations varied from a low of 0 mg./100 c.c. three hours after the initial dose to a high of 21 mg./100 c.c. on the fourth day of therapy. On this regime, the blood concentrations were so variable between individual patients that one cannot state a definite concentration that would be accurate or would apply to the different cases. It was noted that some patients consistently had a high level of free sulfamerazine in the blood, whereas other patients whose blood was drawn and analyzed at the same time constantly had a much lower concentration of the drug in the blood. However, the clinical response to treatment was the same in both types of cases. This marked variability in concentration may be explained partially on the individual ability of the patient to absorb the drug and the amount of urine excreted daily. Too, the administration of sodium bicarbonate to alkalinize the urine results in the relative inhibition of the reabsorption of sulfamerazine by the renal tubules and consequent lowering of the plasma concentration of sulfamerazine. It is also known that, in some cases, the individual being treated did not take any or took only a portion of each dose of the drug which would further tend to confuse the results. An attempt to correlate the intake and output with the concentrations obtained was unsuccessful. Some cases showing a high daily intake and output had a high concentration of the drug in the blood, whereas others on a much lower intake with a lower output had low concentrations.

In this series of cases, twenty-seven of the patients received no sodium bicarbonate or potassium citrate with the sulfamerazine to alkalize the urine. It is worthy of note that no toxic reactions as manifested by hematuria, loin pain, psychosis, leucopenia, nausea and vomiting, or dermatitis were encountered, with or without alkalinization, in this study. Only one patient could be considered to have had toxic symptoms from the drug, and that consisted of a low-grade fever which subsided when the drug was discontinued.

Thus, in résumé, we find sulfamerazine to be an effective, practically nontoxic sulfonamide in the treatment of postabortal and puerperal sepsis. High blood concentrations of the drug are attained more readily and maintained longer with less of the drug than with the more commonly used sulfonamides.

Hunt[23] employed sulfadiazine in several cases of hyperpyrexia occurring in the first five puerperal days. He noted that if the doses administered were from 6 to 8 Gm. per day for two days the therapeutic blood level of the drug was 16 to 20 mg./100 c.c. A maintenance dose of about 6 Gm. per day of the drug was continued until the patient was afebrile several days, unless the drug had to be discontinued because of the occurrence of toxic symptoms. Sinykin,[24] using sulfadiazine in the treatment of puerperal and postabortal infections, found that a blood level of 10 to 15 mg./100 c.c. was usually attained with an initial dose of 3 to 4 Gm. of the drug, followed by 1 Gm. every four hours for the first twenty-four hours and 1 Gm. every six hours thereafter.

Summary and Conclusions

Sulfamerazine was used in the treatment of eighty-eight cases of sepsis complicating abortion and the puerperium. The majority of these patients had endometritis following delivery. From a clinical standpoint, sulfamerazine compares favorably with the more commonly used sulfonamides, and appears to be approximately as effective as sulfadiazine in its therapeutic results. However, it was noted in a few cases that, whereas sulfamerazine manifested a definite bacteriostatic effect, in that the patient did not have a further rise in fever, the fever did not subside and penicillin would have to be used to supplement the drug.

These findings compare favorably with the results obtained on similar cases in which sulfadiazine was used. A review of cases treated with sulfadiazine also showed variability in the amount of the drug used and the period of time it was employed, depending on the response of the patient to chemotherapy and the severity of the infection. Here, too, it was noted that penicillin was occasionally used to supplement the treatment. The usual dosage of sulfadiazine was about 20 to 30 Gm. over a 4-to-5-day period.

From a pharmacological standpoint, high blood levels are obtained rapidly and maintained over a long period of time using either a small dose of sulfamerazine every four hours (½ Gm.) or the usual amount (1 Gm.) of the drug every six hours.

Finally, as a result of this study, the most marked characteristic of sulfamerazine is its practically nonexistent toxicity, as evidenced by only one questionable case of mild toxicity out of eighty-eight cases in which the drug was used. This low toxicity of sulfamerazine is apparent whether one employs an alkalinization agent with the drug or omits it.

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HORMONAL ASSAYS IN A CASE OF HYDATIDIFORM MOLE

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THE value of hormonal assays in the diagnosis of hydatidiform mole and of chorio-carcinoma has been well established.[1, 2, 3, and others]

We wish to present a case of hydatidiform mole in association with bilateral ovarian lutein cysts in which hormonal analyses of some of the body fluids were performed.

Case Report

E. H., a 26-year-old white woman, was admitted to Beth-El Hospital with a history of vaginal bleeding and staining of four weeks' duration. Her last menstrual period was thirteen weeks prior to admission. A previous pregnancy and delivery had been normal. No history of menstrual disorder was elicited. Examination revealed an enlarged uterus reaching to a level of 2 fingerbreadths below the umbilicus. On the second day of admission a Friedman test was positive. A high level of urinary gonadotrophin was found on bioassay. After bleeding ceased the patient was discharged.

The patient was readmitted twenty-two days later with recurrence of vaginal staining of one week's duration. The urinary gonadotrophin had not decreased, indicating the presence of hydatidiform mole. At operation, the uterus was found to be enlarged to the size of a six months' gestation. Both ovaries were large and cystic.

The pertinent data are summarized as follows:

8/18/46—last menstrual flow
10/26/46—onset of vaginal bleeding
11/27/46—Friedman test positive
12/ 2/46—Urine: gonadotrophin* greater than 100,000 M.U./L.
12/30/46—Urine: gonadotrophin* greater than 100,000 M.U./L.
1/ 2/47—Supravaginal hysterectomy and bilateral salpingo-oophorectomy
Cerebro-spinal fluid—gonadotrophin*—5,000 M.U./L.
Ovarian cyst fluid—gonadotrophin* 125,000 M.U./L.
estrogen—negative
1/ 3/47—Serum: gonadotrophin* greater than 333 R.U./100 c.c.
1/ 6/47—Urine: gonadotrophin* all mice died
1/20/47—Urine: gonadotrophin* less than 10,000 M.U./L. (lowest level assayed)
2/25/47—Urine: gonadotrophin FSH reaction—1,000 M.U./L.
LH reaction—less than 666 M.U./L.
(lowest level assayed)

Pathological Report

Gross Description.—Specimen consisted of a supracervically amputated uterus measuring 15 by 15 by 8 cm. The serosa was smooth and glistening. The myometrium was markedly thickened to a maximum of 4 cm. and appeared markedly edematous. Upon opening the endometrial cavity, a large amount of partially necrotic grayish-red tissue was seen, together with numerous grapelike translucent whitish and yellowish nodules which were

*Follicle-stimulating hormone and luteinizing hormone reactions.

limited to the uterine lumen. In addition, a large number of similar grapelike structures had been removed from the uterine cavity. The aggregate diameter of the combined nodules removed from the cavity was approximately 20 cm. On section, the uterine decidua was seen to be thickened and measured 0.7 cm. in width. It presented a serrated margin and separated the underlying myometrium from the grapelike nodules mentioned above. No evidence of penetration of the myometrium by neoplastic tissue was present. Also included were both Fallopian tubes and ovaries. The ovaries were moderately enlarged and each measured 9 cm. in greatest diameter. The surface was glistening and lobulated. Numerous cystic structures protruded above the ovarian serosa. Most of these cysts were filled with a thin, amber-colored fluid but some contained bloody material. Sections of the ovary revealed numerous cysts averaging 1 cm. in diameter (Fig. 1). Many of these cysts contained a thin linear yellowish zone external to the cyst lumen. The Fallopian tubes were thin and patent throughout.

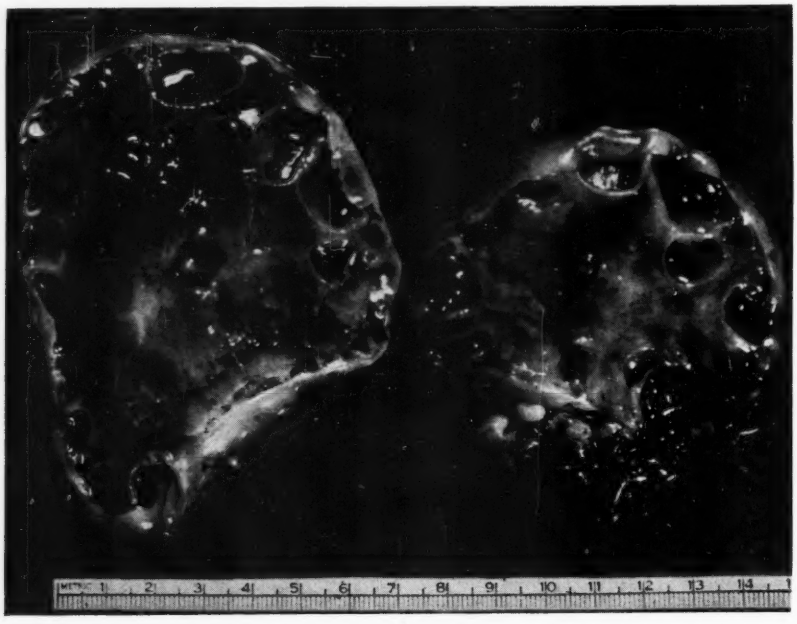

Fig. 1.—Hemisection through both ovaries showing numerous cysts. A prominent broad yellow lining is seen in the cyst at the upper pole of the larger ovary.

Microscopic Description.—Sections through the mole tissue revealed giant chorionic villi which were the seat of edema and focal calcification. The epithelial coverings of the villi showed moderate hyperplastic changes but no atypical cells were found. There was no penetration of the myometrium by trophoblastic tissue. Sections through the ovarian cysts revealed a prominent lutein-cell layer which appeared to arise in part from the theca interna and in part from the granulosa layer (Figs. 2, 3). In the large majority of cysts, the theca-interna layer had been transformed into luteinized cells. An occasional cyst lumen contained abundant hemorrhage.

Methods

The urinary gonadotrophins were assayed by the following modification of the Zondek method: a fresh morning specimen of urine is appropriately diluted with distilled water and injected into immature female mice, 20 to 21 days old and weighing 8 to 10 Gm. Five injections of 0.2 c.c. each are given over a period of three days. The animals are autopsied

on the fifth day and ovarian and uterine changes noted. Follicle maturation and uterine size are used as end points for FSH reaction, whereas presence of hemorrhagic follicles or luteinization indicate the LH effect. The serum gonadotrophins were assayed according to the method of Smith and Smith.[4]

The gonadotrophin content of cerebrospinal fluid and ovarian cyst fluid were determined in the same manner as in the case of the urine.

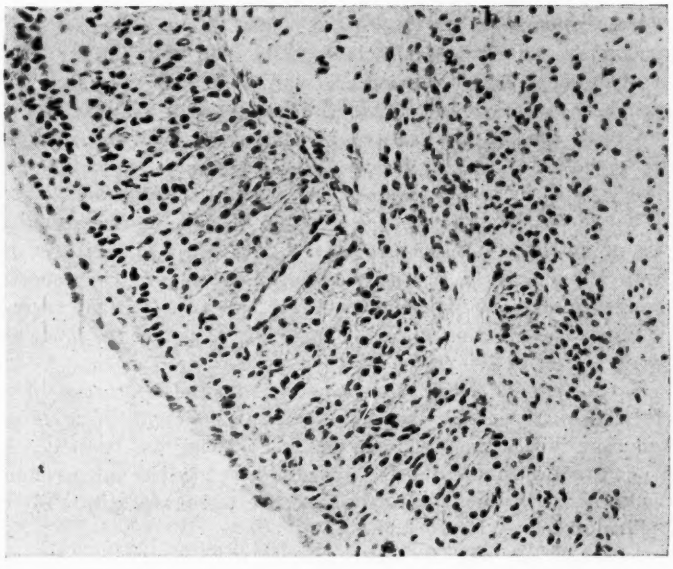

Fig. 2.—Lining of ovarian cyst showing luteinization of both granulosal and internal thecal layers.

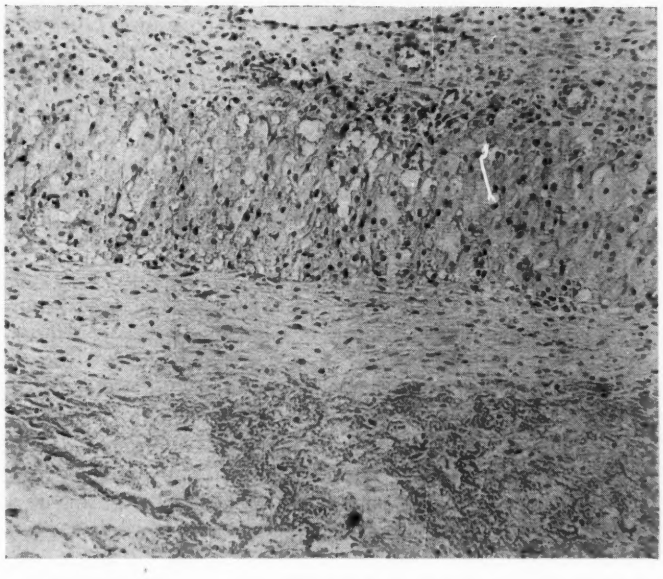

Fig. 3.—Lining of hemorrhagic cyst to demonstrate lutein change in theca interna. The elongated spindle cells adjacent to the hemorrhage are fibroblastic in nature.

Estrogens assays were performed on castrated female rats, which had been previously standardized with respect to response to estrone. Each of three animals was injected three times in a period of two days at different dose levels. Estrus reaction as noted in the vaginal smear fifty-four hours after the first injection indicated a positive response.

Discussion

According to the criteria of Zondek,[1] a urinary level of at least 200,000 M.U./L. of luteinizing gonadotrophic factor is necessary for the diagnosis of hydatidiform mole. In our case, the bioassay revealed more than 100,000 M.U./L. on repeated examinations. Unfortunately, the titrations were not carried through to their endpoints.

It was felt that these high values were significant for several reasons. First, the peak of gonadotrophin excretion in normal pregnancy occurs about the thirtieth to the fiftieth day after the expected but missed menstrual period[5] and our assays were performed at a time beyond this point. Second, the excretion of gonadotrophin remained at a high level for one month. The diagnosis of hydatid mole was confirmed at operation and was subsequently supported by the presence of 5,000 M.U./L. in the spinal fluid.

The presence of multiple lutein cysts of the ovary in hydatidiform mole and choriocarcinoma has been noted early and confirmed in many cases. The reported incidence of these ovarian changes is extremely variable. Mathieu,[6] in a critical review of the literature, quotes estimates ranging from normal ovaries in 95 per cent of the cases, to ovaries affected to a varying degree in 100 per cent of the cases.

Adair and Watts,[7] summarizing eleven cases from the literature in which hormonal assays were performed on the ovarian cyst fluid in cases of hydatidiform mole and choriocarcinoma, showed that in all cases gonadotrophic hormone was present. In our case, the gonadotrophin concentration in the ovarian cyst fluid was in the same range as the urinary level. This is comprehensible on the basis that the tissues of the body will reflect the serum gonadotrophin level.

Zondek[2] described a case of hydatidiform mole with bilateral ovarian cysts in which assay of urinary gonadotrophins showed a positive Aschheim-Zondek test ninety-two days after extrusion of the uterine contents. One week following aspiration of the cyst of one ovary, the Aschheim-Zondek test was negative and remained so. The author suggested the possibility of gonadotrophic hormone being elaborated in the ovarian cyst. There are several groups of observations which would not support this view. Philipp,[8] Lepper et al.[9] and Watts and Adair[7] have shown that the fluid of any type of ovarian cyst associated with pregnancy contains varying amounts of gonadotrophic hormone. The amounts were lower than those found in cases of hydatidiform mole but these figures are indices of the level of gonadotrophins in the body tissues and fluid generally. This would tend to eliminate the cells lining the luteal cysts as the source of the hormone. The presence of gonadotrophic hormone in some cases of paraovarian cysts and in the fluid of "cystic fibroid of the uterus"[7] in cases of pregnancy constitutes further evidence against Zondek's suggestion.

A case somewhat similar to that of Zondek's was reported by Mandelstamm (quoted by Mathieu[6]) in which a positive Friedman test was found in association with persistent multiple lutein cysts of the ovary after the evacuation of the chorionic tissue from the uterus.

In other words, the hormone apparently is stored in, but not elaborated by the cyst. After removal of all mole tissue, the interval during which a positive pregnancy test would be found would depend upon the rate of release of the gonadotrophic hormone from the cyst. This concept is further supported by the clinical evidence that the longer the presence of the hydatidiform mole, the larger will the lutein cysts be[6] and the presence of these cysts is usually accompanied by a longer interval of high urinary gonadotrophin following extrusion of the chorionic tissue.[2]

In this connection, those cases of persistent corpus luteum causing positive pregnancy test reaction are of interest (Israel[10]). One may postulate that the increased urinary gonadotrophin level in these cases is due to the persistent corpus luteum. However, it is

more likely, on the basis of the findings in chorionic disease, that the pathological condition of the ovaries is the result of the high gonadotrophin levels present.

It is generally held that the ovarian changes in hydatidiform mole or choriocarcinoma are the result of intense stimulation of the ovary by the chorionic gonadotrophins present in excessive amounts. The mechanism, however, is vague. Novak[11] and Lazard and Kliman[12] believe that the effect is mediated via the anterior lobe of the pituitary gland. The former author believes that the human ovary does not respond to chorionic gonadotropin and that the changes found in hydatidiform mole are more like those produced experimentally by anterior pituitary hormones. Selye[13] considers the ovarian changes a result of the combined action of gonadotrophins and estrogens.

Summary

A case of hydatidiform mole is reported. The gonadotrophin concentration in the urine, spinal fluid, and fluid of the ovarian lutein cysts was found to be markedly elevated.

Of interest is the reporting of an additional case of histologically verified ovarian lutein cyst formation in association with hydatidiform mole.

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EFFECT OF SULFONAMIDE CREAM ON THE BACTERIAL FLORA OF THE INFECTED VAGINA AND CERVIX

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THE presence of many organisms including lactobacilli, staphylococci, aerobic and anaerobic cocci, colon bacilli, diphtheroids, etc., in both the healthy and infected vagina and cervix has been established by various authors.[1, 2] Whether these organisms (except for Beta hemolytic streptococci, Type A) in the vagina are actual or potential pathogens is still controversial. Two chief factors obscure the evaluation of the findings:

1. Many of the investigations were performed without the aid of modern bacteriological methods. Reliance has been placed largely on stained smears and the determination of the "Reinheit grade."[3] Thorough bacteriologic studies to identify every type of organism present have been rare. Recently Hite, Hesseltine, and Goldstein[4] have excellently performed such a study and concisely reviewed the available literature. Furthermore, many studies have been specifically orientated to the determination of those pathogenic organisms recovered from the vagina associated with puerperal sepsis, trichomonas or monilial infections, or tubal or tubovarian disease.

2. It is difficult to establish the pathogenicity of many of the bacteria isolated without extensive biological study. Additionally, the role of "bacterial synergism" in producing virulent genital infections has not been satisfactorily explored.

A knowledge of the bacterial flora of the vagina and cervix has value in the control and analysis of the more serious types of pelvic infections. Although many bacteriologists state that the vagina and cervix rarely harbor virulent organisms, a not inconsiderable number of studies indicate that bacteria present in the lower genital tract may produce serious lesions of the upper genital tract under special circumstances of abortion, parturition, or gonorrheal infections.[5-8]

Accordingly, it was felt that a study of the bacterial flora of the vagina and cervix of patients complaining of nonspecific leucorrhea, i.e., discharge in the absence of trichomonads, monilia, and gonococci, would be of value. At the same time the effect of sulfonamide cream on the bacterial flora of these cases was evaluated.

Greenblatt[9] suggested that the sulfonamides administered to patients with trichomoniasis diminished the number of commensal bacteria. Siegler[10] reported similar results. Roblee[11] stated that sulfonamide jelly was most effective in the clinical cure of nonspecific vaginitis and following conization of the cervix. His studies were based on the "Reinheit grade." Allen and Baum[12] noted that sulfonamide jellies eradicated cocci from the vagina.

Method

Forty-five patients were studied, all of whom complained of discharge. Examination of the discharge was negative for trichomonads, monilia, and gonococci. In 43 patients, the leucorrhea was associated with varying degrees of cervical erosion. One patient had had a total hysterectomy and one patient was a child with discharge that had resisted other forms of therapy.

Bacteriologic Studies

Secretions from the vagina and cervix were obtained by means of sterile applicator swabs and immediately placed into test tubes containing 1.5 ml. Proteose peptone No. 3 broth.* In the laboratory the swabs were gently pressed against the inner sides of the test tube to mix the secretion with the broth. The swabs were then removed and discarded. The broth was immediately cultured on:

(a) Tryptose blood agar plates†
(b) McConkey's agar‡
(c) Thioglycollate medium§
(d) Sabouraud's dextrose agar,‖ 2 plates

The Tryptose blood agar plates were incubated aerobically at 37° C. and examined after 48 hours and then again after 72 hours.

The McConkey plates were incubated aerobically at 37° C. and examined within 24 hours. The presence of lactose fermenters and nonlactose fermenters were noted and recorded. Nonlactose fermenters were transferred to Kligler's iron agar slants¶ for further identification.

One Sabouraud dextrose plate was incubated at room temperature and the other at 37° C. They were examined during the 48 to 72 hour period for fungi. Suspicious colonies were transferred to corn meal agar# for the study of mycelium and/or ascospore formation.

The thioglycollate medium was incubated aerobically at 37° C. and examined for 72 hours and again after five days. After carefully recording the flora seen on smear examination (Gram's stain) the culture was streaked on:

(a) Tryptose blood agar plate, incubated aerobically at 37° C.
(b) Tryptose blood agar plate, incubated anaerobically at 37° C. using the "chromium-sulphuric acid" method devised by Rosenthal.**
(c) Tryptose blood agar plate, prepared according to the method of Snieszko†† and incubated at 37° C.
(d) Trypsin digest agar‡‡ for lactobacilli. Plates were placed into a candle jar and incubated at 37° C. for 48 hours. They were then examined for the presence of lactobacilli.

Microorganisms which failed to grow on tryptose blood agar (incubated aerobically at 37° C.) but which grew on the Snieszko plates were considered *microaerophiles*. Microorganisms which failed to grow both on the aerobic tryptose blood agar plate and the Snieszko plates but which grew anaerobically by means of Rosenthal's method were considered strict anaerobes.

In 35 patients, at the initial visit, cultures were taken and the patient instructed in the use of a multiple sulfonamide cream.§§ One plunger (4 c.c.) of

*Consists of 2 per cent proteose, Peptone No. 3 (Difco Laboratories) and 0.5 per cent sodium chloride.

†Bacto Tryptose blood agar base (Difco) with the addition of 8 per cent human citrated blood.

‡Obtained from Difco Laboratories.

§Obtained from Baltimore Biological Laboratory.

‖¶#Obtained from Difco Laboratories.

**Rosenthal, L.: "Chromium—sulphuric acid" method for anaerobic cultures. J. Bact. 34: 317-320, 1937.

††Snieszko, S.: The growth of anaerobic bacteria in Petri dish cultures, Zentrabl. f. Bakt. (Abt. 2) 82: 110, 1930.

‡‡Obtained from Difco Laboratories.

§§Generously supplied as "Triple Sulfa cream" by Ortho Pharmaceutical Corp.

cream was inserted by the patient daily for one week and a second culture was obtained. She continued the use of the cream for one more week, at which time, after two weeks of daily therapy, a final culture was made. In ten patients, after initial cultures were taken, the cervix was cauterized. The routine was otherwise unaltered, the cream being used daily and cultures taken at weekly intervals on two occasions.

Results

Twenty-seven microorganisms were recovered from the vaginal and cervical discharge of 45 patients with "nonspecific leucorrhea." The number of times each organism was isolated prior to and following the use of a multiple sulfonamide cream is presented in Table I.

If the isolation of bacteria from the vagina or cervix on any of the three cultures is tabulated for these 45 patients, *Staphylococcus albus* was recovered in 42 cases, gamma streptococcus in 39; diphtheroids, colon bacillus, and alpha-streptococcus each in 26; and beta hemolytic streptococcus in 19. These six bacteria were the most frequent. At least three of these six organisms were recovered together in 40 patients; in five cases, only two were isolated. The number of organisms cultured in any single patient varied from three to twelve with an average of seven different varieties of bacteria. Anaerobic streptococci were rarely encountered.

TABLE I. INCIDENCE OF FLORA IN VAGINA AND CERVIX BEFORE AND AFTER THERAPY WITH "TRIPLE SULFA CREAM"

MICROORGANISMS	VAGINA		CERVIX	
	BEFORE THERAPY	AFTER THERAPY	BEFORE THERAPY	AFTER THERAPY
Aerobes.—				
Staphylococci				
Albus	32	20	32	21
Aureus nonhemolyticus	4	2	4	1
Aureus hemolyticus	1	0	0	0
Gaffkya	1	2	2	3
Streptococci				
Alpha	13	9	13	9
Beta	17	1	15	2
Gamma	29	22	25	20
Diphtheroids	21	12	19	9
B. Coli	16	14	8	10
Aerobacter aerogenes	3	1	1	0
Alkaligenes faecalis	5	1	4	1
Paracolon bacilli	2	1	2	1
Pseudomonas sp.	2	0	1	0
Proteus sp.	1	0	1	0
Hemophilus sp.	15	8	18	10
B. Subtlis	2	1	2	1
Saccharomyces sp.	2	1	1	0
Monilia sp.	3	5	3	5
Microaerophiles.—				
Streptococci				
Alpha	2	0	2	0
Gamma	1	0	3	0
Actinomyces sp.	2	2	1	0
Lactobacilli	6	7	2	6
Anaerobes.—				
Bacteroides sp.	4	4	3	5
Micrococci sp.	0	0	1	0
Streptococci				
Gamma	1	1	1	1
Clostridium sp.	1	1	1	1

Complete tables are not presented because of space limitations and, therefore, change in the density of bacterial growth cannot be graphically presented.

In general, however, there was a marked diminution in the number of total bacterial colonies present on the plates after therapy. The most dramatic response was of beta hemolytic streptococci, which was initially present in seventeen instances and was completely eradicated in fifteen. Unfortunately, at this time, Lancefeld Typing was not performed. The other varieties of streptococci did not respond as completely, although marked diminution in the number of colonies was noted. The number of staphylococci tended to diminish as well, although complete eradication was rarely attained. Little influence was noted on the diphtheroids and coliform groups. The hemophilus species responded erratically—in about half, suppression was noted. As might be expected, lactobacilli were not generally of heavy growth, and some tendency toward growth was noted after inhibition of other species. The other organisms were too few to evaluate the result of treatment.

The clinical results may be summarized as follows:

1. Of ten patients who were cauterized and subsequently treated with a multiple sulfonamide cream, all were cured of the erosion and discharge. The absence of the usual postcautery discharge and bleeding was very striking.
2. Fifteen other patients noted complete or marked relief of discharge. One had had a total hysterectomy and one was a child with a discharge resistant to other forms of therapy. In the remaining thirteen, no significant influence was noted on the cervical erosion even though the subjective symptom of discharge was cured.
3. Twenty patients had no appreciable relief of symptoms and no change in the appearance of the cervical erosion. At the present time, no correlation can be drawn between the changes in the bacterial flora and the clinical results noted.

Summary

1. The incidence of bacteria found in the vaginal and cervical secretions of patients with "nonspecific leucorrhea," excluding those with trichomonas, monilia, or gonorrheal infection, is presented. Twenty-seven microorganisms were isolated, of which the most frequent were *staphylococcus albus;* alpha, beta, and gamma streptococci, diphtheroids, and colon bacilli. The variety of organisms isolated in any single patient varied from three to twelve, with an average of seven. Anaerobic streptococci were relatively rare.

2. A multiple sulfonamide cream is effective in suppressing the coccal organisms and ineffectual in eradicating diphtheroids and coliform species from vaginal and cervical secretions. When used in ten patients after cauterization, it gave striking diminution in postcautery discharge and bleeding. In thirty-five other patients, fifteen noted relief of discharge following three weeks of daily therapy with the cream alone. No improvement of the cervical erosions could be demonstrated within this period.

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PREGNANCY SUBSEQUENT TO RADICAL MASTECTOMY OF THE BREAST FOR CANCER

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IN DETERMINING the advisability of pregnancy subsequent to radical surgery of the breast for cancer, several factors must be taken into consideration. It is important to know:

1. The original pathological report.
2. The classification and degree of malignancy of the tumor.
3. The presence or absence of axillary involvement.
4. The time interval during which the patient has been free from symptoms or metastases since the radical mastectomy.
5. The time which has elapsed since the radical removal of the breast and subsequent pregnancy.

While simultaneous occurrence of breast cancer and pregnancy is relatively rare, as is pregnancy subsequent to radical breast surgery, it is natural to suppose that the latter will confront physicians more often in the future. This will occur as a greater number of women seek medical attention early enough to allow surgery to proceed before the malignancy has metastasized and while there is reasonable chance for five- to ten-year cures. It will be this increasing number of women, who have been free from recurrence of the tumor or metastases, who will be in apparent good health and subsequently become pregnant or want to become pregnant.

Most authors are in agreement that a better prognosis may be given if:

1. The patient has a breast cancer which has been treated by surgery before a pregnancy occurs.
2. No axillary lymph nodes are involved.
3. Subsequent pregnancy does not occur for a period of three or more years.

In view of this general opinion and the increasing number of women who have apparent cures of one or more years and, therefore, may become pregnant, the four following cases of pregnancy subsequent to radical mastectomy for carcinoma of the breast are presented to add to the larger series already studied by Harrington,[5] Smith,[16] Bromeis,[1, 2] Nölle,[10] Kettunen,[7] and others.

CASE 1.—Mrs. M., white, aged 29 years, was admitted to hospital March 15, 1935.

Chief complaint: swelling in the left breast and bleeding nipple.

Three weeks previous to admission she noticed a lump the size of a walnut and two weeks later she began to have bleeding from the nipple.

Examination showed a young, well-developed woman. Right breast—revealed no tenderness or masses. Left breast—in the medial portion slightly below the level of the nipple there was a firm mass about 1 inch by 1 inch by 1 inch. It was not attached to

the chest wall or skin and was freely movable. The mass was tender and on palpation a dark brownish fluid exuded from the nipple.

On March 17, 1935, a radical mastectomy was done.

Pathological examination showed: "Villous duct adenocarcinoma confined to the mass near the nipple. Remainder of breast tissue showed some dilatation of ducts. Axillary tissue showed no evidence of malignancy."

The patient's convalescence was uneventful and she was discharged on March 26, 1935.

Five years later (1940) she was seen, now in her third month of pregnancy. Her prenatal course was uneventful and she delivered spontaneously. She was again seen in 1948 and is in apparent good health.

CASE 2.—Mrs. C., white, aged 28 years, was admitted to hospital April 3, 1944.

Chief complaint: small nodule in left breast.

The patient noticed a small nodule in the outer quadrant of her left breast four days previous to admission. Nodule removed, size 4 by 3 by 2 cm.

Pathological examination showed: "Benign fibroadenoma."

Patient discharged April 4, 1944. Within thirteen months the patient noticed a small nodule in the scar line and returned to her surgeon. She was re-admitted to hospital May 22, 1945, and a semiradical amputation of the left breast was done.

Pathological examination showed: "Adenocarcinoma." Five glands taken from fatty tissue and edge of muscle ranging from 0.5 to 1 cm. in diameter showed metastatic evidence of adenocarcinoma.

Patient discharged June 2, 1945, and was then given a full course of deep x-ray therapy. She was examined in March, 1946, at which time there was no clinical evidence of recurrence of the malignancy. In January, 1947, the patient was again seen and was about two months pregnant and the estimated due date was Aug. 30, 1947. There was no evidence of metastases at this time. Her pregnancy was uneventful until six weeks before the expected date of confinement. At that time she began to complain of sacroiliac discomfort and limped slightly with her left leg. X-rays of the pelvis early in August revealed no bone metastases. Patient delivered a full-term infant in late August. Post partum she continued to complain of sacroiliac pain and a marked secondary anemia persisted despite antianemia therapy. Her symptoms persisted and she was admitted to the hospital in October. X-ray revealed metastases to left hip, back, and skull. The patient expired in December with metastatic carcinoma of the lungs.

CASE 3.—Mrs. T., white, aged 23 years, was admitted to hospital April 2, 1939.

Chief complaint: lump in left breast.

The patient first noticed a tender lump in her left breast two weeks previous to admission. The lump had not changed in size as far as she knew.

Examination revealed a well-developed young woman. Right breast—normal. Left breast—showed the presence of a small lump the size of a marble in the outer upper quadrant, freely movable, not tender.

The tumor was excised.

Pathological examination showed: ovoid mass of tissue measuring 26 by 20 by 15 mm. In the central portion of the tissue there was a firm mass which at one point had a tendency to irregular infiltration of the tissue. Diagnosis: Hyperplastic adenoma with malignant degeneration.

The patient refused further surgical treatment but had eighteen deep x-ray treatments immediately following operation. She was re-admitted June 26, 1939, with the complaint of a hardened area in the right lower part of the left breast below the previous scar. A radical mastectomy was performed.

Pathological examination showed: "Chronic mastitis with lymphocystic and plasma-cell infiltration. Benign fibrous involution. No evidence of malignancy."

Seven years later (1946) the patient became pregnant and delivered a full-term normal infant. In January, 1948, she delivered another full-term normal infant. To date there has been no clinical evidence of breast cancer and the patient is in apparent good health.

CASE 4.—Mrs. H., white, aged 27 years, was admitted to hospital in December, 1938.

Chief complaint: lump in the right breast.

Several weeks previous to admission, the patient had first noticed a lump in her right breast which, in the past month, had increased in size until it was the size of a plum. She had had one pregnancy ten years previous to admission. Two years prior to admission, a simple cyst had been removed from her left breast.

Examination revealed a young, well-developed woman. Right breast, showed a lump about 4 by 4 by 3 cm. in the outer upper quadrant, freely movable, not tender, but of indefinite outline; not attached to skin of structures beneath the mass. Left breast—no tenderness or masses. Small 1½ inch scar present below nipple.

On Dec. 4, 1938, a frozen section showed malignancy and a radical breast amputation was done.

Pathological examination showed: a mass 6 by 6 by 4 cm. present in the breast tissue, not encapsulated. An area at the periphery showed adenocarcinoma; the other areas showed fibrous tissue; dilated ductules. Axillary lymph nodes showed acute hyperplasia—no sign of metastases. Diagnosis: Adenocarcinoma of right breast.

Six years later, in 1944, the patient became pregnant and delivered a normal full-term infant without complications. She was examined in 1947, showed no clinical evidence of metastases, and was in apparent good health.

Of the four cases presented, three are now free from symptoms and metastases. The important factors common to the three cases are:

1. A radical mastectomy for carcinoma was done.
2. There was no involvement of the axillary nodes at operation.
3. Pregnancy followed radical breast amputation.
4. There was a time interval between surgery and pregnancy of more than five years.

In the fourth case, where metastatic involvement occurred, the tumor had a greater degree of malignancy, the time interval between surgery and subsequent pregnancy was relatively short, and the clinical course was progressively bad.

In reviewing the literature as to the question of pregnancy following radical mastectomy for carcinoma of the breast, a marked difference of opinion is found. Rosenthal,[14] Weibel, Redwitz,[19] Reidel, and others believe that pregnancy will activate any cancer growth present and hasten the fatal outcome.

Bromeis[2] and Nölle[10] have found that pregnancy following radical mastectomy does not as a rule lead to local recurrence of the lesion, but that there is a greater danger of formation of a new, primary cancer in the other breast. Gusnar[18] found this true and added the opinion that if the patient had had a previous pregnancy in conjunction with carcinoma of the breast, there was a greater tendency to local recurrences as well as a greater incidence of a second primary lesion in the other breast.

The three cases substantiate Harrington's[5] conclusions based on his series of 4,682 cancers of the breast, in which 55 patients who had been operated upon for carcinoma of the breast subsequently became pregnant. He found that patients who have been operated upon for malignant disease of the breast can

survive a full-term pregnancy for a number of years without recurrence of cancer, and that the number of years of apparent freedom depend on the malignancy of the lesion, the degree of axillary involvement, and the time interval between surgery and subsequent pregnancy.

Conclusions

1. A more favorable prognosis may be given to patients who have had radical surgery of breast for cancer and have subsequently become pregnant after an interval of five or more years.

2. Where there was metastatic spread to the axillary nodes before surgery was done and where there was a subsequent pregnancy in less than four years, the clinical course was progressively downhill.

3. In the four cases presented, there was no evidence of a greater tendency for a new primary cancer in the other breast to develop.

4. Patients adequately treated for early carcinoma of the breast and not having a subsequent pregnancy for four or more years may have apparent freedom from recurrence of the cancer and symptoms for five or more years.

These conclusions suggest the basis for treatment in the type of case presented. More definite conclusions cannot be stated, not only because of the small series of cases presented but because three out of the four cases had all the advantages for a most favorable prognosis. It is hoped, however, that the information given will be of help to those who are confronted with the management of similar cases.

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CYLINDROMA OF THE CERVIX WITH PROCIDENTIA

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COMPLETE prolapse of the uterus complicated by carcinoma of the cervix is an uncommon condition. In 1943, Harvey and Ritchie[7] reported finding only 78 cases in the English literature. We are reporting a case of complete prolapse in which the cervix contained a squamous-cell carcinoma, Grade 3, in situ, associated with an infiltrating adenocarcinoma (cylindroma type). We were unable to find any other recorded case of cylindroma of the cervix in the literature.

Bauer and Fox[1] credited Billroth with coining the term "cylindroma" in 1856, to refer to the peculiar stroma of the tumor. Cylindromas are seen most commonly in the salivary glands, and comprise 15 to 20 per cent of the tumors of these glands.[3] There is no way of differentiating cylindromas from mixed tumors of the salivary glands on gross examination. The microscopic picture, however, is characteristic. There are plugs or cylinders of small hyperchromatic tumor cells in a fibrous or hyaline stroma. The plugs are often "honeycombed," and these central spaces may contain mucus or hyaline substance which represents attempts at acinar formation. At the periphery the plugs often show some degree of palisading of the nuclei. Infiltration of nerves is a characteristic feature of many of these tumors. According to Quattlebaum, Dockerty, and Mayo,[9] cylindromas of the salivary glands have a marked tendency to recur and metastasize, and the prognosis for patients who have this lesion is poor. Cylindromas elsewhere, however, are more benign in nature. Steinmann[10] recorded four cases of cylindroma of the ethmoid region and stated that cylindromas are benign, but frequently recur locally. Bauer and Fox reported three cases of this tumor in the palatal mucous glands, and stated that they are benign but may become cancerous. McDonald[8] reported cylindromas of the trachea and bronchus as a type of slowly growing adenocarcinoma. Fossel[5] reported one case of cylindroma of the vulva in which cure followed local excision.

Report of Case

A white woman, aged 67 years, came to the Mayo Clinic April 20, 1948, because of vaginal bleeding which she had had for one month. Two siblings had died of carcinoma of the stomach.

The patient had had typhoid fever and malaria at 10 years of age. Her two pregnancies went to term. In 1903, at 22 years of age, bilateral oophorectomy had been done for diseased ovaries. This was followed by cessation of menses and menopausal symptoms. For thirty years the uterus had prolapsed outside the vagina but otherwise she was well until one month prior to entry to the clinic. At that time she had noticed the onset of vaginal bleeding. The blood was bright red; bleeding occurred intermittently and varied from slight to profuse.

Physical examination revealed a well-developed and well-nourished woman. General examination gave negative results except for blood pressure of 160/90. Pelvic examination revealed complete prolapse of the uterus associated with cystocele, Grade 4, and rectocele, Grade

4. (Grading in this paper is on a basis of 1 to 4.) On the posterior lip of the cervix was a small, discrete, firm, white lesion, which bled on probing. Laboratory examinations revealed 13.9 Gm. of hemoglobin per 100 c.c. of blood. The leucocyte count was 5,500 cells per c.mm. Flocculation test for syphilis gave negative results. Pyuria, Grade 1, was noted on examination of a voided specimen of urine. Roentgenograms of the chest revealed nothing abnormal.

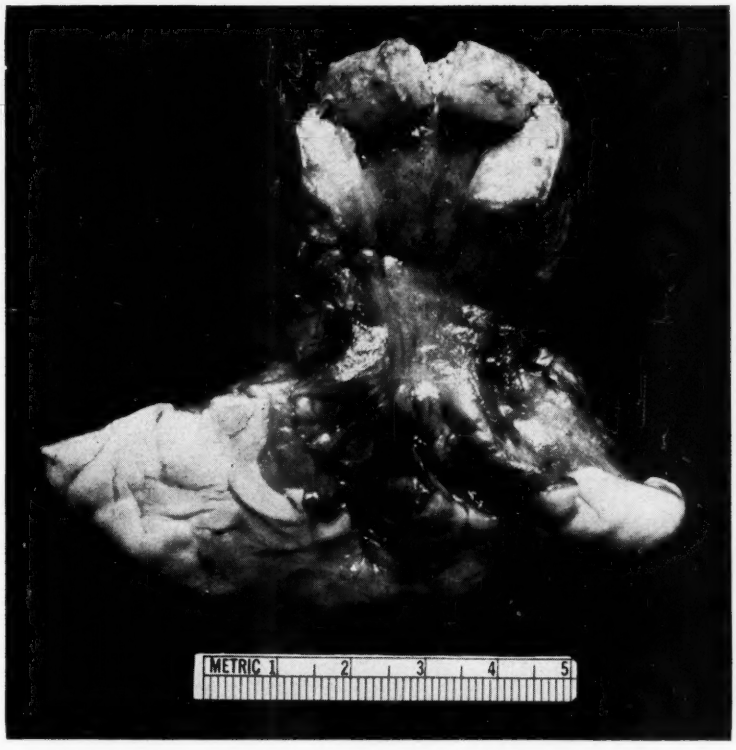

Fig. 1.—Atrophic uterus and small nodule in cervix.

On April 28, 1948, vaginal hysterectomy was performed, and the cystocele and rectocele were repaired. The pathologic specimen showed an atrophic uterus (Fig. 1). At the external os was a nodule measuring 1.5 cm. in diameter. The mucosa over this nodule appeared to be intact. The nodule was circumscribed and pinkish in appearance. On histologic examination, this nodule proved to be an adenocarcinoma of the cylindroma type. It was characterized by regular roundish cells which contained a small amount of cytoplasm. These cells were grouped in the typical cylindromatous pattern which most characteristically resembles the cut surface of Swiss cheese. In this pattern the cells enclosed multiple spaces, roundish to oval in shape, of a regular size. These spaces contained a secretion. Between the masses of neoplastic cells was fibrous tissue (Fig. 2). The epithelium overlying this neoplasm showed a noninfiltrative type of squamous-cell carcinoma, Grade 3, or carcinoma in situ (Fig. 3).

The patient made an uneventful recovery from the operation and was dismissed from the hospital on the sixteenth postoperative day.

Comment

That carcinoma of the cervix associated with complete prolapse is a rare occurrence is evident from the few reports in the literature. In 1932, Guthrie and Bache[6] received 48 replies to questionnaires about this condition sent to

gynecologists and general surgeons in the United States. Of these, 28 (58.3 per cent) had never seen a case, 11 had seen one case and 9 had seen two or more cases. Judd's[6] reply to this questionnaire stated that he had found three cases among 2,188 cases of procidentia of the uterus at the Mayo Clinic, an incidence

Fig. 2.

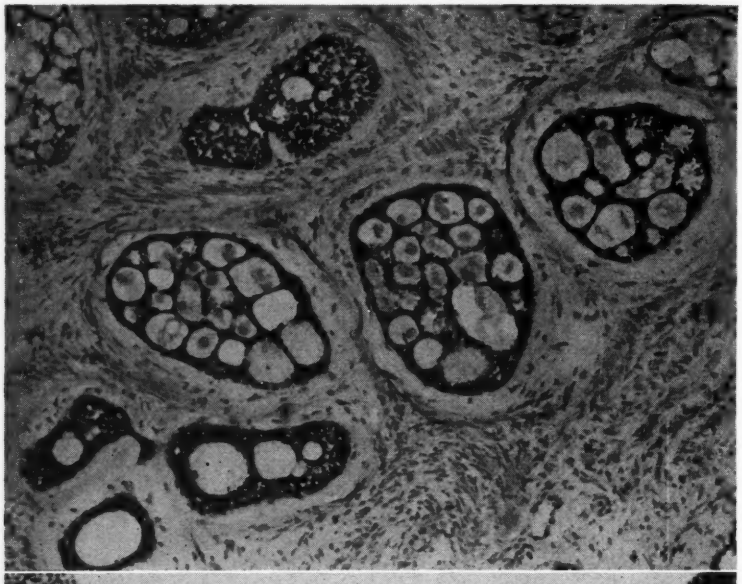

Fig. 3.

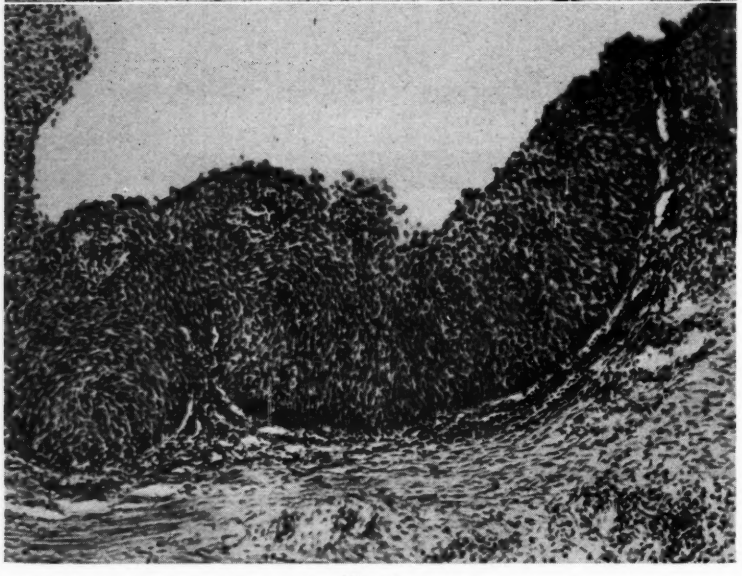

Fig. 2.—Microscopic pattern of the cylindroma (hematoxylin and eosin, ×100).
Fig. 3.—The squamous-cell carcinoma in situ (hematoxylin and eosin, ×100).

of 0.14 per cent. Seven cases of squamous-cell epithelioma of the cervix associated with prolapse of the uterus were found in the files of the Mayo Clinic in the years 1935 to 1947, inclusive. This gives an incidence of between 0.1 and 0.2 per cent of the cases of procidentia which agrees with the incidence reported

by Judd. Of these 7 cases, 5 were found to be cases of carcinoma in situ (intra-epithelial carcinoma). The other two were cases of early, infiltrating squamous-cell epitheliomas of the cervix, Stage I (classification of extent of growth on basis of I to IV). Emmert and Taussig[4] reported four cases, all of which were squamous-cell epitheliomas. In 77 of the 78 cases reported by Harvey and Ritchie,[7] epidermoid carcinoma was present, and in one case a sarcoma.

The reasons given for the rarity of this condition are numerous. Some protection may be afforded by the cornification of cervical epithelium which occurs when the cervix is outside the vagina. Indeed, cervices in cases of procidentia have less areas of infection than the average cervix. There is also less vaginal secretion and relatively more free drainage. Usually uterine prolapse develops later in life than does cervical carcinoma. Women with prolapse often seek medical treatment earlier in the course than patients who have carcinoma. These last two factors did not hold true in the case reported herein. Definite reasons for the unusualness of this condition cannot be stated.

Vaginal hysterectomy seems to be the treatment most favored for cervical carcinoma in prolapsed uteri. At the same time coexisting cystocele and rectocele may be repaired. In view of the fact that most of these tumors are either early Stage I lesions or actually carcinomas in situ, this choice seems justified. However, Harvey and Ritchie favored radium therapy first, with subsequent operation if needed. Boukalik[2] reported one case in which treatment with radium alone resulted in cure of the prolapse and no evidence of recurrence of the carcinoma eleven and a half years after treatment. If, as a result of clinical examination and biopsy, the carcinoma is thought to have spread beyond the cervix, radium therapy would seem to be the more rational approach to the problem.

Summary

Prolapse of the uterus complicated by carcinoma of the cervix is a rare condition. In the case of this type reported, vaginal hysterectomy and repair of vaginal relaxation were employed. The tumor proved to be an adenocarcinoma of cylindroma type. No other cases of cylindroma of the cervix were found in the literature. Vaginal hysterectomy is probably the treatment of choice in cases of prolapse of the uterus and carcinoma of the cervix if the cervical tumor is definitely a carcinoma in situ or of Stage I. Radium therapy should be used first if the carcinoma has extended beyond the cervix.

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II. HYALURONIDASE IN TREATMENT OF HUMAN STERILITY: ALLERGIC REACTION*

LEO H. CRIEP, M.D., AND RALPH E. TAFEL, M.D., PITTSBURGH, PA.

HYALURONIDASE, an enzyme capable of hydrolyzing hyaluronic acid, has attained moderately widespread use in the treatment of sterility. Doubtful as its value in this connection seems to be, it is thought worth while to report a case of a local reaction encountered during its clinical application.

The enzyme hyaluronidase, a so-called "spreading factor," has been recommended in the treatment of human sterility by Kurzrok et al.[1] who have reported favorable results. The theoretical basis for the trial of hyaluronidase in this work rests upon several biological considerations,[2, 3, 4] most important of which is the fact that the enzyme is said to be capable of causing dispersal of the follicular cells of recently ovulated mammalian ova. The use of hyaluronidase implies acceptance of the belief that this disintegration of the corona is a prerequisite to fertilization of an ovum. It is not within the scope of this report to discuss the rationale or practicality of this employment of the enzyme. The method has not been successful in the hands of one of the authors of this paper (R. E. T.).

The hyaluronidase which was used in the treatment of sterility was derived from bovine testes. The bull testis hyaluronidase was provided by Schering and Co. It is protein in nature, and contains inorganic phosphorus and organic sulfur. One of us (R. E. T.) has collaborated in the experimental treatment of a series of 35 women. The technique in most instances was that suggested by Kurzrok, namely, the packing of 10 mg. of hyaluronidase into the cervix near to ovulation time, this application followed by intercourse within a few hours. Of the 35 women to whom a total of 90 treatments were administered, one complained of a troublesome local reaction following each of three cervical applications of the enzyme. None of the other patients experienced such discomfort.

Case Report

Patient E. S., a white housewife, aged 40 years, married for 17 years, with a history of primary sterility, received three applications of hyaluronidase, one each on April 4, May 2, and May 24, 1947, by cervical packing. The reaction consisted of local irritation, oozing, and itching of the vagina and the external genitals. There were also general malaise, abdominal aching and cramping, some coughing, sneezing and lacrimation after each treatment. The reaction occurred in each instance sometime during the night a few hours after intercourse. The cervical application of hyaluronidase in each case was made about four o'clock in the afternoon. The patient herself believes that it is not the material itself that produces the irritation but rather intercourse with probable dispersal following the introduction of the material. It is noteworthy that reaction occurred after each administration of hyaluronidase including the first.

It was proposed to treat the patient with Pyribenzamine before the next treatment with hyaluronidase. The administration of Pyribenzamine, however, was followed by a

*Second of three papers on hyaluronidase studies from the John C. Oliver Memorial Research Foundation and the Departments of Obstetrics-Gynecology, and of Urology, St. Margaret Memorial Hospital, Pittsburgh, Pa.

marked skin eruption, and further applications of hyaluronidase were not attempted. The patient also states that she has been troubled for the last ten years with pruritus ani and has had various treatments for this condition without favorable results. However, this was not made worse during the course of the vaginal reactions to hyaluronidase.

The patient gives no history of any allergic manifestations, such as asthma, hay fever, hives, or eczema. There is no family history of allergy.

Intradermal tests with various dilutions of hyaluronidase extract gave uniformly negative results. Passive transfer was negative. A patch test performed on the skin close to the external genitals was negative; a scratch patch test with this material in the same area was slightly positive. The application of a small amount of hyaluronidase to the vaginal mucosa caused considerable irritation and exudation within a short time.

Comment

A case of local contact dermatitis due to bull testis hyaluronidase is herewith reported. Apparently hyaluronidase is not a primary sensitizer. This case must be considered one of allergic type of eczematous contact dermatitis. The possibility of an atopic factor responsible for the respiratory symptoms must also be considered, even though the intradermal tests were negative.

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Department of Reviews and Abstracts

Selected Abstracts

Cancer, Malignancies

Stokes, E. Malcolm: The Association of Estrogenic Administration and Adenocarcinoma of the Endometrium, West. J. Surg., page 494, Sept., 1948.

A carcinogen is a chemical or physical substance which applied under certain conditions induces a malignant tumor. Estrogen, chemically related to polycyclic hydrocarbons, is a carcinogen. Neoplastic cells arise from foci where rapid cell division is occurring in response to a repair or regeneration stimulus. When some external factor is introduced which interferes with the maturation of the normal cell enzyme pattern, the cells revert to the embryonic type. There is evidence to suggest that the estrogens accelerate such a reversion, possibly through their effects upon cell protoplasmic enzyme maturation.

There was a Negro woman, aged 65 years, 19 years postmenopausal, who received 470 doses of 0.1 mg. of stilbestrol over a period of 21 months. The uterus enlarged progressively and at operation an endometrial polyp with adenocarcinoma was found. It is the long, continuous administration of small estrogen doses that is more apt to cause carcinoma than the larger doses administered over shorter periods. WILLIAM BICKERS.

Cabrera, G., and Guzman, F.: Sarcoma of the Fallopian Tube. Clinical Case Report, Bol. Soc. chilena de obst. y ginec. 13: 64-67, May, 1948.

The authors describe a rare case of primary sarcoma of the Fallopian tube in a 59-year-old patient with history of 8 deliveries and two spontaneous abortions. Her menopause occurred at age of 56 years. Pain and six days of vaginal bleeding were the first symptoms. She gained 13 kilograms in eight months. The tumor on the right tube measured 8.0 cm. in diameter and the microscopic diagnosis was sarcoma of the tube. Because of peritoneal implantations the patient received radiotherapy subsequent to surgery. CLAIR E. FOLSOME.

Vergara, C. Casarin: Uterine Fibroids and Fundal Carcinoma, Ginec. y obst. de Mexico 3: 115-128, April, 1948.

Vergara reviews 4,012 operative cases seen in Pavillion 25 of the General Hospital in Mexico City between October, 1938, and August, 1947. Among these were 410 cases of uterine fibroids treated surgically. Ten of these cases, 2.5 per cent, presented coexisting adenocarcinomas of the fundus uteri.

The author concludes that any woman who bleeds in menopause should submit to hysterography and endometrial biopsy although preferably a diagnostic dilatation and curettage. His treatment recommendation includes total hysterectomy.

The article includes three tables and fourteen illustrations. The photographs of thirteen hysterograms are striking in their bizarre shadows and illustrate well the intrauterine patterns of coexistent fibroids and corporal carcinoma. CLAIR E. FOLSOME.

Endocrinology

Rauramo, Lauri: The Level of Tocopherol (Vitamin E) in Blood Serum and Milk. The Values of Serum Tocopherol During Pregnancy and Lactation, Acta obst. et gynec. Scandinav. **27:** Supplement 2, 1947.

The author completes an important contribution on tocopherol (Vitamin E) in its relation to pregnancy and lactation, in the dual departments of Biochemistry and Obstetrics and Gynecology at Helsinki University. His well-documented and extensive bibliographic report first reviews the influence of Vitamin E on tissue growth and hormone influences in laboratory animals. He then surveys numerous methods to evaluate tocopherol in blood serum and milk. To attain a greater degree of accuracy with microchemical methods he originates a new modification of the Emmerie-Engel dipyridylfenichloride test and an original revision of Kofler's chromatographic adsorption procedure. In the latter he describes a more prolonged extraction method as well as a mechanical separation of the fluorescent portion of the chromatogram.

In his series of 53 nonpregnant women he noted 512 gamma per cent tocopherol value. Among the small group of normal mates the tocopherol value was found to be 416 gamma per cent. Tocopherol values were obtained throughout various phases of the menstrual cycle in the nonpregnant women. No significant changes were found related to any phase of the cycle.

Serum tocopherol values increased in the course of pregnancy gradually on a slowly climbing curve from the nonpregnant value of 513 gamma per cent up to an average of 1,131 gamma per cent immediately before delivery in a series of 32 pregnant women. There was only a slight fall during the first week after delivery, with an average value of 992 gamma per cent at the seventh postpartum day in the blood serum of sixteen women. During the first two months of nursing the serum tocopherol values returned gradually to nonpregnant figures but continued nursing reduces still more the serum tocopherol levels to an average of 300 gamma per cent. Large babies or sex of babies showed no reflection in the tocopherol serum level of the nursing mother.

The author, comparing his findings to serum level of tocopherol in nonpregnant cases in Holland and America, found lower figures in Holland and America than in Sweden. On the other hand he did find that the serum tocopherol level of pregnant women was the same value in Sweden and Holland.

One unique finding was that the tocopherol value in mother's milk was very high on the first day of nursing, varying from 1,000 to 3,480 gamma per cent in the first four days of nursing, but within 25 days from delivery the tocopherol content in maternal milk was generally under 300 gamma per cent.

The serum tocopherol average values in cows was 446 gamma per cent; for bulls 337 gamma per cent; for horses 156 gamma per cent and for pigs 85 gamma per cent. Rauramo was unable to find, with his methods, any measurable quantities of tocopherol in cow or goat milk being sold in Sweden.

Sixteen excellently prepared tables and a well-organized method of presenting his evidence in his 77-page study assist the reader in following the observations with ease.

CLAIRE E. FOLSOME.

Nunez, A. Clavero: The Use of Estrogens in the Differential Diagnosis of Metrorrhagias, Revista Portuguesa de Obstetricia, Gincologia e Cirurgia **1:** 189-190, June, 1948.

The author states that the bleeding from metropathia hemorrhagica can be distinguished easily from bleeding from incomplete abortion by injecting, in a single dose, 150,000 I. U. of dihydrofolliculin benzoate or any other natural estrogen of similar activity. If it is a question of metropathia hemorrhagica the bleeding lessens several hours later and ceases entirely the day following. The same method applies to menopausal bleeding which ceases if there is no organic pathology.

CLAIR E. FOLSOME.

Endometriosis

Gori, R. M.: Tubal Endometriosis, Endosalpingosis, Obst. y ginec. latino-am. **7:** 242-264, June, 1948.

Gori restudied the pathology of Fallopian tubes taken from 862 patients over a period of twenty-five years in the Gynecology Clinic of Medical School of Buenos Aires. Among these cases the tubes showed no involvement in 146 instances; 24 cases of acute salpingitis; 16 subacute, and 291 cases of chronic salpingitis; 67 cases showing a tubercular process; 192 cases in which the tubes showed sequelae from chronic inflammatory change; 118 instances of tubal pregnancy; 4 cases of primary tubal carcinoma; 2 cases of hemorrhagic infarction, and one case each of actinomycosis and lymphosarcoma of the tubes. Among the 862 cases were found 77 patients showing endometriosis or endosalpingosis, an incidence of 8.9 per cent of the tubes examined.

The distribution of the endometriotic processes in the tubes were listed in the following groups: involvement of the interstitial portion and isthmus of the tube, 22 cases; involvement of the ampullar and distal end of the tube, 15 cases; diffuse process in the tube, 3 cases; peritoneal portion of the tube, 6 cases; endosalpingosis of the interstitial and isthmus of the tube, 16 cases; endosalpingosis of the ampullar and distal region of the tube, 8 cases; and endometriotic processes in tubal pregnancies, in 10 cases. Endometriosis was found in 5.9 per cent and endosalpingosis in 3.0 per cent of the cases; the former was found most often in the fourth decade and the latter diagnosis in the fifth decade. Dysmenorrhea was present in 73.6 per cent of the cases having endosalpingosis and in 45.9 per cent of the patients with endometriosis. The closer the endometriotic process was found to the uterus the greater was the incidence of dysmenorrhea as a symptom. Sterility was present in 52.1 per cent of the cases having endometriosis in the internal portion of the tubes as compared to 62 per cent sterility in patients having endosalpingitis. Uterine fibroids were found in 50 per cent of the series. Other localizations of the process besides the tube were found in 36 per cent of the cases. Among 113 tubal pregnancies, endometriotic lesions were found in 9.7 per cent of the series and in this group of tubal pregnancies there were 37.6 per cent of the group having associated fibroids. The author regards the Philipp and Huber modified theory of Sampson as the most logical to explain the pathogenesis of these processes. Seven tables and an unusually comprehensive bibliography accompany the article. CLAIR E. FOLSOME.

Brocq, Pierre: The Status of Endometriosis in Gynecology, Rev. brasil. de cir. **17:** 289-296, June, 1948.

Since certain well-known French authorities still fail to recognize the entity of endometriosis, the author, a professor at the Paris Medical School, deems the subject worthy of factual review. First, he cites the pathological findings in the genital tissues, where endometriosis is much more frequently found, and then adds his observations anent the paragenital and extragenital findings in an excellent guest editorial. In the extragenital group he describes the lesions in the following order of frequency—the rectum, sigmoid, appendix, and the small intestines in the intestinal group; elsewhere, by order of frequency, the lesions are seen on the round ligament, the inguinal canal, laparotomy scars, perineal areas, and on the umbilicus. He cites three unusual cases of endometriosis located respectively on the thigh, the elbow, and the anterior surface of the forearm. He cites several cases, from the literature, that were most troublesome to explain from the pathogenic viewpoint; e.g., Gander's case of endometriosis of the scrotum in a male operated upon for hernia. The latter author mentions a similar second case in his article.

The author then considers endometriosis from the clinical viewpoint of the gynecologist, the surgeon, and the histologist. The surgeon generally regards these lesions as uncommon. The gynecologist regards it as essentially a pathological state seen frequently with other gynecologic conditions but primarily as a lesion producing the symptom of secondary dysmenorrhea. The pathologist decrees the poorer term endometrioma while the term adenomyo-

sis can be used only when we are aware of specific pathological findings. Endometritis is an incorrect tem. When considered in light of the metaplastic theory of pathogenesis the term *gynoblasts* would indicate those undifferentiated uterine cells capable of undergoing metaplastic change into endometrial elements. While the writer reviews in detail the theories and facts of the implantation and metaplasia hypotheses, and further cites a case he reported earlier with Varangot and Aschheim, wherein they found glandular elements in the veins of the myometrium during surgical care of a fibroid, the author believes that one cannot dismiss entirely the metaplasia theory. He cites Robert Meyer's suggestion that while endometrial fragments are capable, under selective influence, of destroying the musculo-elastic walls of vessels, they never pass the endothelial barriers.

In conclusion Brocq states that endometriosis, unrecognized by our forefathers, has a vastly distinctive position in our nosology. It should not be included either in the inflammatory states or the new growth categories. It is primarily a dysfunction related to increased estrogenic activity. As such it can be treated in two ways: by castration in the serious cases, or else by hormonal therapy in those exhibiting lesser symptomatology.

CLAIR E. FOLSOME.

Burnside, Alfred F.: An Evaluation of the Treatment of Endometriosis, South. Surgeon, page 645, Sept., 1948.

Endometriosis, its etiology, and treatment continue to be the object of speculation and theories. The author accepts the conclusions of Sampson that desquamated endometrial cells at the time of menstruation can regurgitate through the tubes and implant on the peritoneum. In support of the transplantation theory attention is called to certain cases of endometriosis in the abdominal wall following cesarean section.

Prophylactic measures which may be taken to prevent or stay the progress of endometriosis are correction of retroversion, dilatation of a stenosis, myomectomy, and discarding instruments during operation which have come in contact with the endometrium. Advanced pelvic endometriosis may be treated by x-ray which is often preferable to surgery. Limited experience with tesosterone prompts the author to recommend it. Personal experiences in the treatment of this disease are cited which add nothing to the knowledge of the subject.

WILLIAM BICKERS.

Gynecologic Operations

Ahltorp, Gideon: On Conservative Myomectomy. A Clinical and Statistical Investigation of the Indications and Technique Used, and the Results Obtained in Conservative Operations for Fibromyomas of the Uterus, Acta obst. et gynec. Scandinav. **26:** Supplement 6, 1946.

Ahltorp surveys 282 cases of abdominal myomectomy and 46 cases of vaginal myomectomy done at Upsala University Hospital (1923 to 1931) and the Stockholm General Maternity Hospital (1931 to 1941). His 238-page report represents a classic on this important subject. He found conservative myomectomy used in less than 10 per cent of the total number of abdominal operations for fibroids. In a comparison of results of the conservative myomectomy to 572 cases of radical abdominal operations for fibroids, in the same period, the results of the former were more favorable. There was no mortality in the group operated upon conservatively and a 2.0 per cent mortality in the hysterectomized group.

Of 161 women undergoing enucleation of fibroids, 121, or 75.2 per cent, were free of recurrence. The risk of recurrence was found greater in cases where more than four fibroids were shelled out but even these percentages decrease as the increasing age of the patient is considered. Eight of the 242 cases of enucleation were reoperated upon (3.3 per cent). Seventy-five per cent of the patients treated conservatively had relief from menstrual distress. Thirty-three of 250 cases operated upon by conservative abdominal method afterward be-

came pregnant; however, only 93 of the group of 250 had a conceivable chance of pregnancy, making the percentage incidence 31.0 per cent. Among the 33 women having pregnancies, there was a total of 51 pregnancies, of which 33 went to term, three to premature delivery and fifteen resulted in miscarriage. In total, the mothers in this group gave birth to 36 living infants and one stillborn child. Spontaneous delivery occurred in 29 instances, forceps in five, and section was done on only one mother.

In five of the married women having conservative myomectomy, there was a history of three to fifteen years of preceding sterility. All these patients became pregnant within a year after surgery.

The author concludes that the uterus should be, as far as possible, left intact during the reproductive age period. He feels that the number of surgeons doing conservative operations for fibroids is increasing, although they are still far outnumbered by those who practice the too common total extirpation and, therefore, needless sacrifice of the uterus. Fifty-four tables and two figures are included in this excellent article which could well be read in detail by more American gynecologists and surgeons. CLAIR E. FOLSOME.

Palmer, Raoul: Instrumentation and Technic of Gynecological Celioscopy, Gynéc. et obst. **46:** 420-431, April, 1947.

Palmer reports his experiences after completing 250 gynecological celioscopies, with no untoward serious complications, and obtaining definite clinical information in 240 cases (96 per cent) in the series. Upon this justification he evaluates the techniques and methods in current use in gynecology. He describes three principal methods: (1) Irving Stein's method of outlining pelvic organs by pneumoperitoneum; (2) Kjellberg's method of introducing 40 to 80 c.c. of radiopaque solution via the transuterotubal route (hysterosalpingo-pelvigraphy) and (3) Decker's culdoscopic method. After using Decker's transvaginal approach, with patient in the knee-chest position, some ten times, Palmer considers it much inferior to the transabdominal celioscopic method for three reasons: (1) the vaginal route is least satisfactory from the point of asepsis; (2) while ovaries and tubes can be examined, the number of additional abdominal fields is limited because of difficult instrumentation through the vagina with patient in the knee-chest position, and (3) it is impossible to section adhesions from vaginal route but easy from the transabdominal route. The author does not summarize his clinical findings save as occasional cases to illustrate points of technique. CLAIR E. FOLSOME.

Thomas, Walter L., Carter, Bayard, and Parker, Roy T.: Radical Panhysterectomy (Wertheim) and Radical Pelvic Lymphadenectomy, South. M. J. **41:** 895, Oct., 1948.

Experience with radical hysterectomy and radical pelvic lymphadenectomy for the treatment of cancer of the cervix has been reviewed. Three groups of patients are compared: (1) patients with no previous irradiation; (2) patients who received x-ray therapy only or radium therapy only; (3) patients who, prior to operation, received complete radium and x-ray therapy. In the first group (44 per cent) there were eight (24 per cent) in whom pelvic lymph node metastases were found. In the second group (37 per cent) there were six (21.4 per cent) with positive nodes, and in the third group (15 per cent) there were two (18.2 per cent) with positive nodes. Microscopic findings in the radiated nodes showed definite evidence of radiation effects and it is probable that the cancer cells were destroyed in many of these lymph nodes before their surgical removal.

Seventy-five patients are reported with no death due to operation. Seven of these patients had adenocarcinoma of the cervix; and in this group it is felt that operation was definitely to be preferred to irradiation therapy. The same may be said for squamous-cell carcinoma of the cervical stump and squamous-cell carcinoma of the cervix complicated by early pregnancy. The majority of patients with carcinoma of the cervix will continue to be treated with the accepted techniques of irradiation therapy, but there is a small group in whom the surgical approach is preferred. WILLIAM BICKERS.

Labor, Management, Complications

Abbas, T. M.: The importance of External Hysterography in the Study of Uterine Activity, Edinburgh M. J., page 423, July, 1948.

The author presents several tracings of uterine activity made with a modified Dodek's tachodynamometer. One tracing of antenatal uterine activity confirms the findings of Murphy by demonstrating the large alpha waves and the small beta waves present prior to the onset of labor. Stimulation of the postpartum uterus with pituitary extract and physiologically at the time of nursing are also demonstrated. The irregularity of the contractions in uterine inertia is shown. Morphine reduced the amplitude and rate of uterine contractions in eight out of ten cases. Pethidine, on the other hand, increased the rate and progressively magnified the amplitude of the individual contractions in seven cases. In three cases, however, the contractions were not altered. L. M. HELLMAN.

Beruti, J. A., Tenconi, J. L., and Tenconi, E.: A New Contribution to the Study of Transverse and Oblique Presentations, Archivos de la Clinica Obstetrica y Ginecologica "Eliseo Canton" **2:** 349-365, Sept., 1943.

The authors classify the transverse and oblique fetal presentations into eight groups: dorsoanterior, posterior, superior, inferior, anterosuperior, posterosuperior, anteroinferior, and posteroinferior. To provide experimental roentgenographic evidence, they took numerous x-rays of a stillborn, placing his back convexly, into varied positions. They then describe seven new cases of transverse presentation and three cases with oblique presentation, with radiological data, from private cases seen in the Eliseo Canton Clinic in Buenos Aires.

The writers consider their studies to be important from a practical clinical management viewpoint. They had fewer diagnostic errors by distinguishing between the dorsosuperior variety and the breech presentation. They indicate that there is a greater tendency for spontaneous correction, with facileness, by external version in some varieties but not in others. In the dorsosuperior presentation there was a tendency to premature rupture of the membranes. Three tracings illustrate the article. CLAIR E. FOLSOME.

Menstruation, Dysmenorrhea

Vignes, Henry: Amenorrhea Among Prisoners, An. brasil. de gynec. **24:** 325-330, November, 1947.

The author, as one of a group of specialists, visited a concentration work camp at Drancy, after the liberation of Paris in September, 1944, sheltering about 9,000 prisoners of whom about 2,000 were women. Among the 676 cases with gynecologic symptoms were 154 instances of menstrual disorder among whom were 22 cases of menometrorrhagia, 128 cases of amenorrhea and four "mixed" cases. The author stresses the significance of emotional change upon the induction of amenorrhea in captive women. CLAIR E. FOLSOME.

Uriegas, G., and Guerrero, C. D.: Anovulatory Menstruation in the Etiology of Sterility, Ginec. y obst. de Mexico **2:** 209-238, June, 1947.

The authors review 105 consecutive cases of primary sterility in women. Among this group they found that 5.71 per cent exhibited anovulatory menstruation. Their criterion for study was based largely upon premenstrual endometrial biopsies. They grouped their series into three categories: group a, showing normal endometria, 43 cases; group b, showing histologic patterns suggesting decreased estrogenic activity but with some secretory activity, 46 cases; and group c, 16 cases, or 15.2 per cent of the series, exhibiting unusually atypical endometria. Among this latter group, six cases were found to have atrophic-like

endometrium, or definite absence of secretory activity to justify the diagnosis of anovulatory menstruation. The remainder of this subgroup (c) all exhibited scant secretory endometrial evidence. The sixteen cases of group (c) are individually documented and nine figures illustrate the article. CLAIR E. FOLSOME.

Bushnell, Lowell F.: The Production of Ovulation in the Anovulatory Patient, West. J. Surg., page 556, Oct., 1948.

Failure to ovulate is assumed after four consecutive cycles of uterine bleeding from a proliferative endometrium and a concurrent basal body temperature curve showing no evidence of a biphasic curve. It is assumed that the anovulatory cycle is the result of either anterior lobe failure or antihormone inhibition. The patient is given 20 units of mare serum, gonadotropin, every 2 days during first half of the cycle and 40 units on the last 14 days of the last half. If a biphasic curve is induced, she is continued on this routine during subsequent months until pregnancy occurs. If biphasic curve does not result the dose may be increased to 50 units utilizing the same dose schedule of treatment. This treatment program may be used in the treatment of secondary amenorrhea, 40 per cent of these patients developing regular cycles after treatment. Administration of chorionic gonadotropin in the last half of the cycle favors luteinization of the endometrium. Approximately 50 per cent of anovulatory patients were induced to ovulate as indicated by thermal shift and endometrial response.
WILLIAM BICKERS.

Benson, Ralph C.: The Effect of Pitressin Tannate in Oil Upon Uterine Bleeding, West. J. Surg., page 440, Aug., 1948.

The physiology of menstruation and the current laboratory and clinical research related to it are presented in one of the best reviews of the subject to appear in recent clinical literature. It is evident from the endometrial transplant experiments of Markee and the anatomical studies upon the spiral end-arteries of the endometrium that menstruation is primarily a vascular phenomenon and more specifically arteriole in nature. The rate of blood flow through endometrial spiral arteries is influenced by myometrial contractions, the tortuosity of the spiral vessels, contraction of the radial arteries, and by the total blood volume passing through the uterine arteries. The volume of blood passing to the uterus can be reduced by means of Pitressin, the vasopressor hormone. Moreover, the nongravid uterus is highly irritable to Pitressin, but relatively nonreactive to Pitocin.

Pitressin tannate in oil was used for treatment of metrorrhagia and polymenorrhea in 100 patients, the dose being 1 c.c. of Pitressin in oil for 3 days. Through its action on the spiral arteries and the myometrium, uterine bleeding irrespective of etiology was successfully controlled in a large number of cases. The hormone is not curative, but most useful in the management of persistent and otherwise uncontrollable bleeding from the nongravid uterus. WILLIAM BICKERS.

Miscellaneous

Van Ravesteyn, L. W.: The Presence of Ascorbic Acid in the Follicular Cells of the Graafian Follicle in the Latter Phase of Development, the Preovulatory Phase, Acta Neerlandica Morphologiae Normalis et Pathological 5: 285-301, 1945.

Van Ravesteyn, working in the Embryology and Histology Laboratory of Utrecht University, selected a special strain of white mice known for their high degree of fertility—47 generations in 9 years and known as the "047 Leeuwenhoekhuis of Amsterdam strain." The animals were sacrificed by decapitation, the ovaries and vagina removed, prepared with special fixatives of 10 per cent silver nitrate in the presence of strong acid (to precipitate in the cells, by reducing the silver salt with sodium bisulfite and light, the ascorbic acid) and then the

tissue is serially sectioned. It is stained by Henke's method to provide more contrasting microphotographs.

The author found that the follicular cells always contain ascorbic acid in the last phase of maturation following the onset of estrus. The amount of ascorbic acid in the follicular cells is decreased slightly a little before ovulation. After ovulation, the ascorbic acid is concentrated, in the beginning, in the inner cell beds before the follicular cells. Following this, the ascorbic acid becomes more prominent in the external cellular beds while the corpus luteum is forming. The theca cells of the follicle contain ascorbic acid during ovulation and the follicular fluid gives, at the onset of the preovulatory phase, a very clear ascorbic acid reaction.

The article is well illustrated with seven microphotographs and well documented by data and bibliography. CLAIR E. FOLSOME.

Portes, L., Granjon, A., and Heuville, A.: Tuberculosis and Twinning, Gynéc. et obst. **46:** 112-115, 1947.

The authors, questioning the older observation that tuberculosis was a factor in twinning, decided to study the problem. From Baudelocque Clinic they reviewed twin cases born of tubercular mothers over the period from 1914 to 1944. They found 36 cases. In the twenty-three-year period, 1921 to 1944, 3,011 tubercular women had been hospitalized after abortion or delivery. Thirty had a history of twin delivery or abortion and one of a triplet abortion, or an incidence of 1.02 per cent of the total pregnancies. In a comparable period in France the twinning incidence was 1.10 to 1.20 per cent. In the same hospital from 1914 to 1944 there were 76,682 nontubercular pregnant cases. Among these were 781 instances of twin delivery or abortion, an incidence of 1.27 per cent.

In 30 years, 36 twin deliveries or abortions among a total of 981 had taken place in tubercular cases, or 3.67 per cent of twin cases. The 3,011 cases of pregnancy with tuberculosis represented 4.83 per cent tuberculosis among the pregnancy series. The authors conclude that tuberculosis is not a factor in twinning.

The prognosis of associated tuberculosis and twin pregnancy was found poor. Maternal mortality was 17.0 per cent in the month following delivery as compared to 2.9 per cent in the nontubercular mothers giving birth to twins. The over-all tubercular maternal mortality was 4.8 per cent. The fetal mortality in tubercular mothers with twins, sixth month of pregnancy to the first thirty days after delivery, was 26.6 per cent, as compared to 20.9 per cent in nontubercular women having twins. CLAIR E. FOLSOME.

Newborn

Wiener, A. S., and Wexler, I. B.: Antenatal Selection of Donors for Exchange Transfusion in Erythroblastosis, Anesthesiology **9:** 296, 1948.

In the treatment of erythroblastosis fetalis, replacement transfusion is employed. If this is to prevent permanent tissue damage, such a transfusion should be given immediately after birth, and it is desirable to select a suitable donor for the transfusion before the birth of the child. This can often be done by determining the blood group of the mother and father. Since the fetus and the newborn infant do not produce antibodies, the only antibodies in the blood of the infant at birth are derived from the mother; the mother's blood group, therefore, is an important consideration. A table is presented showing the blood group from which a donor can be selected when the blood group of the mother and father are determined. In some cases, however, the donor cannot be selected until the infant's blood group is determined from the cord blood. If a compatible donor is not available in cases of great urgency, group O blood to which Witebsky's A and B substance has been added to neutralize the alpha and beta antibodies may be

employed to begin the transfusion, using matched blood to complete transfusion. If the father belongs to group O or A, and as the mother's blood (and therefore the infant's blood) will not contain anti-A agglutinins, a group A, Rh-negative donor can be used for the transfusion without determining the infant's blood group. But the donor cannot be chosen in advance if the mother belongs to group O and the father to group A, as, if the infant was of group O his serum would contain both alpha and beta antibodies and only a group O donor would be suitable; but if the infant belonged to group A, a group O donor could not be used because of alpha agglutinins in such a donor's plasma and a group A donor should be used. Analysis of other combinations, as given in the table, shows that an AB donor can be used for transfusion if the mother is of group AB, whether the father's blood group is O, A, B, or AB.

An illustrative case is reported in which the father was of group A, the mother of group AB, the father Rh-positive (Rh_1 rh) and the mother Rh-negative. Repeated determinations of the anti-Rh agglutinins in the mother's blood showed a rapid rise in titer during pregnancy of antibodies of the agglutinin type. An Rh-negative donor of group AB was selected for transfusion, and labor was induced two weeks before term. A replacement transfusion was given at birth using 500 c.c. of the donor's blood from which half the plasma was withdrawn using saline solution to make up the volume (to reduce the conglutinin content of the blood). The child made a good recovery, and the donor's blood cells survived in the infant's circulation for two months, although the infant was found to belong to group B. HARVEY B. MATTHEWS.

Watson, Janet: The Significance of the Paucity of Sickle Cells in Newborn Negro Infants, Am. J. M. Sc. **215:** 419, April, 1948.

In this communication an hypothesis is advanced to explain why there are relatively few sickle cells to be found in the blood of newborn infants whose blood later exhibits typical sickling.

The blood of 226 consecutive Negro newborn infants was studied. The mothers of these infants were used as controls. Sicklemia was found in eighteen of the mothers and nineteen of the newborns. This corresponds to the usual figure given for sicklemia in this country which is 7.3 per cent. In the series studied, 8 per cent of the mothers and 8.4 per cent of the infants had the disease. That sicklemia is Mendelian dominant is borne out by the fact that nine of the nineteen infants had mothers who also had the trait. Study of the blood of the mothers revealed that 84 to 100 per cent of the red cells showed sickling, whereas there was sickling in only 0.5 per cent to 29.5 per cent of the red cells of the infants. An explanation of the paucity of sickling in fetal blood is that it has been shown that fetal hemoglobin differs from adult hemoglobin. It is thought that this difference between the two is due to a variation in the chemical structure of the globin. Fetal hemoglobin thus appears to lack the sickling properties of adult hemoglobin. To substantiate this theory, studies were continued on infants showing sickling through the first four to six months of life. Since the estimated life span of the erythrocyte is four months, it would be expected that beyond this period of life marked sickling would occur. This is exactly what happened. Intrauterine death from sickle cell anemia has never been observed because fetal hemoglobin is unable to sickle even at the low oxygen tension which exists in the fetus. HERBERT J. SIMON.

Patrick, P. R.: Report of a Survey of Children Born in 1941 With Reference to Congenital Abnormalities Arising From Maternal Rubella, M. J. Australia, vol. I, 35th yr. no. 14, p. 421, 1948.

The types of cases and abnormalities resulting from rubella in the mother contracted during pregnancy are reviewed. The figures continue to prove that the risk is greatest durng the early months of pregnancy. The most frequent abnormality found was deafness;

then followed congenital heart disease, mental deficiency, and finally cataracts. The authors conclude that despite the lack of experimental evidence, there is sufficient clinical evidence in this and other reports to show the grave risk of exposure of the pregnant woman to rubella. Certain preventive measures are outlined to prevent these abnormalities. The treatment and education of the handicapped are also outlined.

WILLIAM BERMAN.

Pregnancy, Complications

O'Hanlon, R. H., and Stewart, F. S.: Maternal Jaundice in Association With Hemolytic Disease Due to Rh Sensitization, Irish J. M. Sc., 1948.

Two cases of coincidental maternal jaundice in Rh sensitization are presented. In one, the mother gave birth to an infant with relatively mild hemolytic disease. In the other, the infant was hydropic. The authors do not establish any causal relationship between the maternal jaundice and hemolytic disease. L. M. HELLMAN.

Whitelaw, M. James: Thiouracil in the Treatment of Hyperthyroidism Complicating Pregnancy and Its Effect on the Human Fetal Thyroid, J. Clin. Endocrinol., November, 1947.

The literature to date of cases of hyperthyroidism, complicated by pregnancy and treated with thiouracil, is reviewed. A case is then reported of a patient exhibiting marked thyrotoxicosis (basal metabolism rate plus 65 per cent) who was hospitalized in her twenty-sixth week of pregnancy. Thiouracil treatment was instituted and continued until the forty-first week of her pregnancy when she delivered an encephalic male monster. The infant survived six hours and ten minutes. After death the thyroid gland was removed. The gland was found to be slightly smaller than the reported normal, there was no diminution of the iodine content, and the histologic appearance was normal.

Thus, it would appear, based on a single case, that the administration of thiouracil to a hyperthyroid pregnant female has no demonstrable injurious effect on the newborn.

HERBERT J. SIMON.

Radiation

Borell, U., Westmann, A., and Orstrom, A.: Studies on the Functions of the Hypophyseal-Diencephalic System and of the Ovaries by Means of Radioactive Phosphorus, Gynaecologia **123:** 186-200, March, 1947.

The authors, reporting from the Gynecology Clinic at Caroline Hospital, Stockholm, determined to find a way to demonstrate the possible role that the nervous centers in the hypothalamus might play in ovarian function beyond the known hypophyseal factors. They selected the rabbit as the best suited experimental animal because the maturation and rupture of the follicles occur only after intercourse or strong sexual stimulus. Radioactive phosphorus as free phosphorus, P^{32}, in 5 per cent glucose solution, was injected intravenously into anestrus and estrus females at predetermined intervals before and after coitus. Castrate animals were also examined three to five weeks after oophorectomy. Each animal received 0.1 mc. in 1.0 c.c. Thirty minutes after injection the animals were killed by decapitation to remove all possible blood from organs. The blood, cerebellum, tuber cinereum, pars glandularis of the hypophysis, and the ovaries were examined for total radioactivity and total phosphate.

For the tuber cinereum, adenohypophysis, and ovaries the authors found no difference in phosphate turnover between the anestrus and estrus female rabbits. In castrate animals they found an appreciable increase in the phosphate turnover in the adenohypophysis and no increase in the tuber cinereum.

There was a rapid increase in the radioactive phosphorus turnover in the hypophyseal-diencephalic system in relation to coition, the increase appearing distinctly in appreciable values in two minutes after coitus. The increased activity is maintained in the tuber cinereum during the first postcoital hour. The pars glandularis of the hypophysis gave an increased activity postcoitally which was maintained for 24 hours with peak activity at the second half-hour period after coition. An increase was demonstrated postcoitally in ovaries but not appearing until thirty minutes after coitus. The high level in ovaries is maintained reaching a new maximal plane in nine to eleven hours after coitus; i.e., when ovulation occurs. Upon the basis of these observations the authors conclude that the hypophyseal-diencephalic system constitutes a functional unit to play a conclusive part in ovulation. CLAIR E. FOLSOME.

Kahanpaa, V.: A New Simplified Radium Applicator for Intensifying the Radiotherapy of the Parametria in Cancer of the Cervix, Acta Radiol. **27:** 495-504, 1946.

Kahanpaa, of the Central Institute for Radiotherapy, Helsinki, develops a new vaginal applicator from stainless steel plate in the shape of a narrow "U." The radium bolts are placed at ends of both distal limbs of the "U" which are bent outwardly. Thise spring tension causes powerful lateral pressure. At the same time a tight Y bandage over the bow end of the applicator pushes the radium-containing bolts higher up into the parametrial regions. This permits a 1,000 mg. hr. greater dosage in vaginal radium treatment than was possible with other applicators because the rectal wall is displaced more effectively out of the way during treatment, thus increasing the ability to deliver a greater parametrial radium dosage via vaginal route. The author, after experience with 35 cases, states the applicator is now part of the regular equipment at their clinic along with the otherwise three-phase method of Stockholm. Ten illustrations are included. CLAIR E. FOLSOME.

Sterility, Fertility, Contraceptives

Chastrusse, M. L.: Artificial Insemination in Woman, J. de méd. de Bordeaux **125:** 1-15, Jan., 1948.

The author reviews the history of insemination in women and animals in a lengthy article. He includes many new references not familiar to American workers in this field. He divides his discussion into numerous headings including (1) the indications; (2) contra-indications; (3) the technique, under which he considers (a) the choice of the donor, (b) evaluation of the semen specimen, (c) the time for insemination, and (d) the technique for introduction of sperm; (4) the legal aspects; (5) the moral aspects and (6) the religious considerations.

The author offers no case studies, only a well-phrased review. His contribution is important because of his discussion of considerable literature not available in the States. In summary, the author condemns heterologous insemination heartily and states homologous insemination is indicated only in organic maldevelopments or previous genital injury in the married couple. The insemination technique should always be only vaginal in type.

CLAIR E. FOLSOME.

Murray, E. G.: Extragenital Pelvic Pathology in Sterility, Ginec. y obst. de Mexico **3:** 167-180, 1948.

Murray, of Buenos Aires, selects from 652 sterility cases, seen at the Sterility Clinic of the Pedro A. Pardo Lying-In Hospital, 66 patients presenting extragenital pelvic pathology which he considers pertinent to the sterility etiology. The author believes that this group of 12.5 per cent of female sterility etiology, the peritoneal factor, is often neglected in case study and treatment. He divides these "blockings" into several categories: ovarian (ovulation precluded by intrinsic or extrinsic layering of resistant fibrous tissue or serosa); tubal

(obstructed fimbria); and peritoneal (malpositions of upper generative organs by adhesions and old adherent exudates). He believes also that there exist functional ''blockings'' when the distance between the ovary and the fimbria is increased due to the retraction of the mesentery of or ligament of the ovary and/or tube.

The author illustrates the value of salpingohysterography in the diagnosis of these ''blocking'' factors. Treatment is usually surgical. Twenty-three cases, 34.8 per cent, were so treated. From this group he has obtained four full-term pregnancies, a success of 17.39 per cent following surgery. Eleven figures illustrate the article. CLAIR E. FOLSOME.

Tubal Insufflation

Nielsen, Povl Holm: Injuries Caused by Hysterosalpingography, Acta obst. et gynec. Scandinav. **26**: 565-597, 1946.

Nielsen, from the University Clinic of the Aarhus Municipal Hospital, Denmark, reviews the experience of hysterosalpingography, with the use of iodized oils only, in his own clinic and from questionnaires sent to one hundred thirteen Danish hospitals excluding only those with ten beds or less. He estimates 12,000 studies were done by the hospital group receiving the questionnaire and 1,098 more were done on 982 patients at his clinic between June 1, 1940, and Sept. 1, 1944.

The one hundred thirteen Danish hospital groups were divided into three classifications: A, departments of obstetrics and gynecology, ten in number; B, forty departments of surgery; and C, sixty one-department hospitals. The three additional questionnaires overlapped radiological groups in larger hospitals with both types of service. In Group A, all used hysterosalpingography and five reported no complications; the five others reported ten, plus ''a few'' cases of flareup of salpingitis or parametritis; and one reported one case of perforation of uterus. In Group B, thirty-three of forty surgery departments used this method and twenty-eight of these had had no complications. The five others reported five re-exacerbations of salpingitis and two fatalities (peritonitis). Among Group C, only thirty-one of the sixty one-department hospitals used the method, while twenty-eight of these had no complications and the remainder reported a scant number of salpingitis recurrences. Only a few hospitals used Lipiodol, most using other iodized oil preparations including Iodipin, Iodumbrin, Perabrodil, Hippodin, or more lately Uroselectan B.

The author found twenty-two patients among his own clinic series of 982 cases (1,098 hysterosalpingograms) exhibiting mild symptoms (mild temperature rise of 0.5 to 1.0 degree) and seven cases with more marked or protracted symptoms. All seven cases had mild to moderate recurrence of salpingitis.

Nielsen concludes that he could find no evidence of iodine intoxication, one case of uterine perforation, five cases of contrast media introduced into uterine vessels, and that he could find no evidence to indicate that hysterosalpingography increased the disposition to extrauterine pregnancy. He further concludes that while the technique is simple, it is not an insignificant intervention, but that its use in clinical gynecology is immensely important. Statistically, the chance for flare-up of inflammatory change is 0.25 per cent, while the chance of death is 0.1 to 0.2 per 1,000. CLAIR E. FOLSOME.

Vaginal Infections

Da Silva Pereira, J. M.: Myiasis of the Vulva, An. brasil. de. gynec. **24**: 331-340, Nov., 1947.

The author presents a review of the rare disease, myiasis of the vulva, and adds a new case to the literature. His case was present in a 17-year-old Negro pregnant woman in her

fifth month of pregnancy. The larvae were studied and diagnosed as those of *Cochliomyia hominivorax*. Treatment consisted of intravenous injections of a mercury compound, Arsenox, and penicillin. Four pictures illustrate the lesion, larvae, and insects. CLAIR E. FOLSOME.

Ferrer, D. Lopez: Some Considerations on Vaginal Trichomoniasis, Ginec. y obst. de Mexico **2**: 451-455, Dec., 1947.

The author reviewed the pelvic findings of 500 consecutive obstetrical and gynecological cases seen at Maximo Avila Camacho Center, Mexico, to evaluate vaginal trichomoniasis. From the 500 cases seen, 437 of them, 87.4 per cent, presented leucorrhea of several types. Of this series 83 women, or 19.2 per cent, had demonstrable trichomonads in their leucorrheal secretions, and while 104 cases of the 437 women having leucorrhea (20.8 per cent) had pruritus, it was found as a symptom in thirty-six instances of the 83 cases (34.61 per cent) having trichomonorrhea.

The patients were treated with silver picrate suppositories with or without acidulated douches for a time interval of eight days to six months. There were two cases refractive to this treatment and none showed intolerance to the local drugs used. The author's breakdown of his figures on the incidence of this infestation and on correlation of symptoms to type of leucorrhea in pregnant and nonpregnant patients is well done. He finds trichomoniasis of greater frequency in pregnant and sterility cases and the symptom of pruritus a more constant finding when this infestation is the chief etiologic factor in leucorrhea.

CLAIR E. FOLSOME.

Chavarria, H. M.: The Treatment of Trichomonas Vaginitis. The Action of Topical Estrogens, Bol. de la Soc. de obst. y ginec. de Buenos Aires **26**: 536-544, Nov. 13, 1947.

The author feels there are cyclic aggressions of trichomonads accounting for increased epithelial destruction periodically. This increased activity of trichomonas seems to occur at periods of lowered estrogen levels. To offer resistance to destruction of the mucosal stratification, he used local estrogenic therapy only in fifty-five cases, all observed over a long period of time. He not only obtained relief in a large number of cases but was able to clear up some unusually resistant cases. He outlines his rationalization in clear terms and this is enlarged upon considerably by numerous discussants of his paper. He relies not entirely upon local estrogens, but deems them important as supplemental local treatment.

CLAIR E. FOLSOME.

Branscomb, Louise: Mycotic Vulvovaginitis, South. M. J. **41**: 534, June, 1948.

Severe itching of the vulva and vagina will often result in micotic infection. Microscopic examination of the vaginal secretion on wet smear often fails to reveal the mycelium or buds, or yeast fungi; while culture on Sabouraud's medium confirms the diagnosis. A simple culture method is described in which the vaginal secretion is allowed to stand in saline for forty-eight hours, during which time the growth of yeast fungus occurs and microscopic detection is facilitated.

Treatment of fifty-one private patients with propionate jelly is described. Vaginal insertion of the jelly twice daily for twenty days was prescribed. A majority were relieved of itching within seventy-two hours and thirty-three were cured at the and of three weeks. Where skin involvement of the vulva is present, propionate jelly is inadequate for cure. It must be supplemented by gentian violet. WILLIAM BICKERS.

Items

The International and Fourth American Congress on Obstetrics and Gynecology

The Scientific and Educational Exhibit Committee of the International and Fourth American Congress on Obstetrics and Gynecology under the Chairmanship of Dr. John Parks of Washington, D. C., and the Committee on Motion Pictures with Dr. Archibald D. Campbell of Montreal, Canada, as Chairman have completed preliminary plans for their respective sections of the meeting and are ready to issue application blanks for space and time. These blanks are designed to facilitate the work of the committees in selecting and presenting exhibits and films of the greatest value and to make it easy for the applicants to present a complete description of their proposed displays. They will be sent on request by the business office of the American Congress at 24 West Ohio Street, Chicago 10, Ill., and, when completed, go directly to the chairman of the committee involved.

The members of the Scientific and Educational Exhibit Committee working with Doctor Parks are: Dr. Miguel V. Falsia of Buenos Aires, Sir Eardley Holland of London, Dr. Mortimer N. Hyams of New York, Dr. Alice F. Maxwell of San Francisco, Dr. Lawrence M. Randall of Rochester, Dr. Jorge de Rezende of Rio de Janeiro, Dr. Erik Rydberg of Copenhagen, Dr. Donald G. Tollefson of Los Angeles, and Dr. Frank E. Whitacre of Memphis.

The members of the Committee on Motion Pictures working with Dr. Campbell are: Dr. David N. Barrows of New York, Dr. Willard R. Cooke of Galveston, Dr. Samuel A. Cosgrove of Jersey City, Dr. Carl Henry Davis of Wilmington, Dr. Ludwig A. Emge of San Francisco, Dr. Albert W. Holman of Portland, Dr. Edmundo G. Murray of Buenos Aires, and Dr. Robert A. Ross of Durham.

The scientific program is in charge of Dr. Howard C. Taylor, 842 Park Avenue, New York City 21, New York, U. S. A. Those desiring to contribute should address him at an early date for further information.

American Board of Obstetrics and Gynecology

The American Board of Obstetrics and Gynecology in annual session in Chicago, Ill., May 8 to 14, 1949, announced the election of the following officers:

Walter T. Dannreuther, M.D., President, New York, N. Y.
Joseph L. Baer, M.D., Vice-President, Chicago, Ill.
Willard R. Cooke, M.D., Vice-President, Galveston, Texas.
Paul Titus, M.D., Secretary-Treasurer, 1015 Highland Building, Pittsburgh, Pa.
Robert L. Faulkner, M.D., Assistant Secretary, 2105 Adelbert Road, Cleveland, Ohio.
The other Directors of the Board are:
F. Bayard Carter, M.D., Duke University, Durham, N. C.
Daniel G. Morton, M.D., University of California Hospital, San Francisco, Calif.
Robert A. Kimbrough, Jr., M.D., 807 Spruce Street, Philadelphia, Pa.
Lawrence M. Randall, M.D., Mayo Clinic, Rochester, Minn.

The next annual examination meeting will be held at the Hotel Shelburne in Atlantic City, New Jersey, May 21 to 28, 1950, immediately following the International Congress on Obstetrics and Gynecology in New York.

ROSTER OF AMERICAN OBSTETRICAL AND GYNECOLOGICAL SOCIETIES*

(Appears in January, April, July, October)

American Gynecological Society. (1876) *President,* Joseph Baer. *Secretary,* Norman F. Miller, 1313 East Ann St., Ann Arbor, Mich. Next meeting, May 11, 12, 13, 1950, The Greenbrier, White Sulphur Springs, Va.

American Association of Obstetricians, Gynecologists and Abdominal Surgeons. (1888) *President,* James R. Bloss, Huntington, W. Va. *Secretary,* Leroy A. Calkins, 418 11th Street, Huntington, W. Va. Annual meeting Hot Springs, Va., Sept. 7-9, 1949.

Central Association of Obstetricians and Gynecologists. (1929) *President,* Earl C. Sage, Omaha, Neb. *Secretary-Treasurer,* John I. Brewer, 104 South Michigan Ave., Chicago, Ill. Annual meeting Oklahoma City, Okla., Nov. 3, 4, and 5, 1949, Municipal Auditorium.

South Atlantic Association of Obstetricians and Gynecologists. (1938) *President,* C. J. Andrews, Norfolk, Va. *Secretary,* E. D. Colvin, 1259 Clifton Road, N.E., Atlanta, Ga. Next meeting, Feb. 9, 10, and 11, 1950, Hotel Roanoke, Roanoke, Va.

A. M. A. Section on Obstetrics and Gynecology. *Chairman,* William F. Mengert, Dallas, Texas. *Secretary,* A. B. Hunt, Mayo Clinic, Rochester, Minn. Annual meeting June, 1950.

New York Obstetrical Society. (1863) *President,* Albert H. Aldridge. *Secretary,* Claude E. Heaton, 205 East 69th St., New York 21, N. Y. Second Tuesday, from October to May, Yale Club.

Obstetrical Society of Philadelphia. (1868) *President,* Carl Bachman. *Secretary,* George A. Hahn, 255 S. 17th St., Philadelphia, Pa. First Thursday, from October to May.

Chicago Gynecological Society. (1878) *President,* Herbert E. Schmitz. *Secretary,* Edward M. Dorr, 30 N. Michigan Ave., Chicago 2, Ill. Third Friday, from October to June, Hotel Knickerbocker.

Brooklyn Gynecological Society. (1890) *President,* Henry S. Acken, Jr. *Secretary,* J. Edward Hall, 429 Clinton Avenue, Brooklyn 5, N. Y. First Friday, from October to May, Kings County Medical Society, 1313 Bedford Ave., Brooklyn, N. Y.

Baltimore Obstetrical and Gynecological Society. (1929) *President,* Houston S. Everett. *Secretary-Treasurer,* W. Drummond Eaton, 11 E. Chase St., Baltimore 2, Md. Meets quarterly at Maryland Chirurgical Faculty Bldg.

Cincinnati Obstetrical Society. (1876) *President,* Edward Friedman. *Secretary,* Lester J. Bossert, 2404 Auburn Ave., Cincinnati 19, Ohio. Third Thursday of each month.

Louisville Obstetrical and Gynecological Society. *President,* Rudy F. Vogt. *Secretary-Treasurer,* Glenn W. Bryant, Louisville, Ky. Meetings fourth Monday of each month from September to May, Brown Hotel.

Portland Society of Obstetrics and Gynecology. *President,* Ronald Frazier. *Secretary-Treasurer,* Gifford D. Seitz, 919 Taylor St. Bldg., Portland 5, Ore. Meetings last Wednesday of each month.

Pittsburgh Obstetrical and Gynecological Society. (1934) *President,* R. A. D. Gillis. *Secretary,* Clarence H. Ingram, Jr., 902 Peoples East End Building, Pittsburgh 6, Pa. First Monday of October, November, December, January, February, March, April, and May.

Obstetrical Society of Boston. (1861) *President,* M. Fletcher Eades. *Secretary,* H. Bristol Nelson, 1180 Beacon Street, Brookline, Mass. Third Tuesday, October to April, Harvard Club.

New England Obstetrical and Gynecological Society. (1929) *President,* Arthur E. G. Edgelow, Springfield, Mass. *Recorder,* Carmi R. Alden, 270 Commonwealth Ave., Boston 16, Mass. Meetings held in May and December.

Pacific Coast Obstetrical and Gynecological Society. (1931) *President,* Philip H. Arnot. *Secretary-Treasurer,* R. Glenn Craig, 490 Post St., San Francisco, Calif.

Washington Gynecological Society. (1933) *President,* Henry L. Darner. *Secretary,* John Parks, 901 23 St., N.W., Washington, D. C. Fourth Saturday, October, November, January, March, May.

New Orleans Obstetrical and Gynecological Society. (1924) *President,* Conrad G. Collins. *Secretary,* E. W. Nelson, 1407 S. Carrollton Ave., New Orleans, La. Meetings held October, November, January, March, and May.

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*Changes, omissions, and corrections should be addressed to the Editor of the JOURNAL. The number after the Society's name is the year of founding.

St. Louis Gynecological Society. (1924) *President,* A. N. Arneson. Secretary, Paul F. Fletcher, 634 North Grand Ave., St. Louis 3, Mo. Meetings second Thursday, October, December, February, and April.

San Francisco Gynecological Society. (1929) *President,* Albert M. Vollmer. *Secretary.* Donald W. de Carle, 2000 Van Ness Ave., San Francisco, Calif. Regular meetings held second Friday in month from October to April, University Club, San Francisco, or Claremont Country Club, Oakland, Calif.

Texas Association of Obstetricians and Gynecologists. (1930) *President,* Julius McIver, Dallas. *Secretary,* George F. Adam, 4115 Fannin St., Houston 4, Tex. Annual meeting, Dallas, Texas, September, 1949.

Michigan Society of Obstetricians and Gynecologists. (1924) (Formerly the Detroit Obstetrical and Gynecological Society.) *President,* O. W. Picard. *Secretary,* Carl F. Shelton, 910 David Broderick Tower, Detroit 26, Mich. Meetings first Tuesday of each month from October to May (inclusive).

Central New York Association of Gynecologists and Obstetricians. (1938) *President,* Louis G. Fournier. *Secretary,* Merton C. Hatch, Medical Arts Bldg., Syracuse, N. Y. Meets second Tuesday of September, November, January, March, and May.

Alabama Association of Obstetricians and Gynecologists. *President,* Gilbert F. Douglas. *Secretary,* Hunter Brown, 1922 South Tenth Ave., Birmingham, Ala.

San Antonio Obstetric Society. *President,* I. T. Cutter. *Secretary,* S. Foster Moore, Jr., San Antonio, Tex. Meetings held first Tuesday of each month at Gunter Hotel.

Seattle Gynecological Society. (1941) *President,* Donald J. Thorp. *Secretary-Treasurer,* Charles D. Kimball, 734 Broadway, Seattle 22, Wash. Meetings held on third Wednesday of each month, Washington Athletic Club.

Denver Gynecological and Obstetrical Society. (1942) *President,* Lyman W. Mason. *Secretary-Treasurer,* Jack M. Simmons, Jr., 638 Republic Bldg., Denver 2, Colo. Meetings held first Monday of every month from October to May (inclusive).

Wisconsin Society of Obstetrics and Gynecology. (1940) *President,* Henry A. Sincock. *Secretary-Treasurer,* Edith McCann, 425 East Wisconsin Ave., Milwaukee 2. Meetings held in May and October.

San Diego Gynecological Society. (1937) *President,* P. L. Martin. *Secretary,* Albert P. Kimball, 233 "A" St., San Diego, Calif. Meetings held on the last Friday of each month.

North Dakota Society of Obstetrics and Gynecology. (1938) *President,* H. A. Wheeler, Grand Forks. *Secretary,* C. B. Darner, Fargo, N. D.

Virginia Obstetrical and Gynecological Society. (1936) *President,* Walter McMann. *Secretary-Treasurer,* L. L. Shamburger, State Health Department, Richmond, Va. Next meeting not announced.

Columbus Obstetric and Gynecologic Society. (1944) *President,* Wayne Brehm. *Secretary,* Zeph J. R. Hollenbeck, 9 Buttles Ave., Columbus, Ohio. Meetings held fourth Wednesday of each month.

Naussau Obstetrical Society. (1944) *President,* Robert S. Millen. *Secretary-Treasurer,* Peter La Mariana, Williston Park, L. I., N. Y. Meetings, bimonthly from October to May.

Bronx Gynecological and Obstetrical Society. (1924) *President,* Charles W. Frank. *Secretary,* Benjamin Karen, 1100 Grand Concourse, New York 56, N. Y. Meetings, fourth Monday monthly from October to May.

Washington State Obstetrical Society. (1936) *President,* John H. Fiorino, Everett. *Secretary,* C. Wendell Knudson, Medical and Dental Bldg., Seattle, Wash. Meetings, first Saturday of April and October.

Kansas City Obstetrical and Gynecological Society. (1922) *President,* Joseph G. Webster. *Secretary,* William C. Mixson, 320 W. 47th St., Kansas City, Mo. Meetings, last Thursday, September, November, January, and March; first Thursday, May, University Club.

Los Angeles Obstetrical and Gynecological Society. (1914) *President,* L. G. Baldwin. *Secretary-Treasurer,* Gordon Rosenblum, 6333 Wilshire Blvd., Los Angeles 36, Calif.

North Carolina Obstetrical and Gynecological Society. (1932) *President,* Wallace B. Brad ford. *Secretary,* Richard B. Dunn. Meetings semiannually.

The Society of Obstetricians and Gynecologists of Canada. (1944) *President,* J. Ross Vant. *Secretary,* J. O. Baker, Edmonton, Alberta. Annual meeting, June 18 to 22, 1949, at Jasper Park Lodge, Jasper National Parks.

Akron Obstetrical and Gynecological Society. (1946) *President,* George A. Palmer. *Secretary-Treasurer,* Alven M. Weil, 1030 First National Tower, Akron 8, Ohio. Meetings held third Friday of January, April, July, and October, City Club of Akron, Ohio, Bldg.

Minnesota Society of Obstetrics and Gynecology. *President,* Russell J. Moe. *Secretary,* John Haugen, 100 E. Franklin, Minneapolis, Minn. Meetings held spring and fall.

Miami Obstetrical and Gynecological Society. (1946) *President,* Homer L. Pearson. *Secretary,* John D. Milton, 1104 Huntington Bldg., Miami, Fla. Meetings, second Thursday in January, March, May, and November.

Omaha Obstetrical and Gynecological Society. (1947) *President,* Harley E. Anderson. *Secretary,* Donald C. Vroman, 813 Medical Arts Bldg., Omaha 2, Neb. Meetings held third Wednesday in January, March, May, September, November.

Oklahoma City Obstetrical and Gynecological Society. (1940) *President,* John W. Records. *Secretary-Treasurer,* Henry G. Bennett, Jr., 800 Northeast 13 Street, Oklahoma City 4.

Cleveland Obstetrical and Gynecological Society. (1947) *President,* Robert E. Faulkner. *Secretary,* G. Keith Folger, 10515 Carnegie Ave. Meetings on fourth Tuesday of September, November, January, March, and May at University Club, 3813 Euclid Ave., Cleveland 15, Ohio.

New Jersey Obstetrical and Gynecological Society. (1947) *President,* Herschel Murphy. *Secretary,* Benjamin Daversa, Spring Lake, N. J. Meetings semiannually.

Honolulu Obstetrical and Gynecological Society. (1947) *President,* Frank C. Spencer. *Secretary-Treasurer,* H. McLeod Patterson, 202 King Kalakaua Bldg., Honolulu, Hawaii. Meetings third Monday of each month, Mabel Smyth Building.

Oregon Society of Obstetricians and Gynecologists. *President,* Gerald Kinzel. *Secretary-Treasurer,* Theodore M. Bischoff, 529 Mayer Bldg., Portland 5, Ore. Meetings held on third Friday of each month from October to May.

National Federation of Obstetric-Gynecologic Societies. (1945) *President,* Ralph E. Campbell. *Secretary,* Woodard D. Beacham, 429 Hutchinson Memorial Bldg., New Orleans 13, La.

Dayton Obstetrical and Gynecological Society. (1937) *President,* A. D. Cook. *Secretary,* L. O. Frederick, 413 Third National Bldg., Dayton 2, Ohio. Meetings, third Wednesday monthly from September through June at the Van Cleve Hotel.

Dallas-Fort Worth Obstetric and Gynecologic Society. (1948) *President,* Asa A. Newsom. *Secretary,* A. W. Diddle, 2211 Oak Lawn Ave., Dallas 4, Texas. Meetings in spring and fall.

Queens Gynecological Society. (1948) *President,* Edward C. Veprovsky. *Secretary,* George Schaefer, 112-25 Queens Blvd., Forest Hills, N. Y. Meetings held second Wednesday in February, April, October, and December, at the Queens County Medical Society Bldg.

Mississippi Association of Obstetricians and Gynecologists. (1947) *President,* Walter Simmons. *Secretary,* Richard H. Street, Jr., The Street Clinic, Vicksburg, Miss. Meetings held semiannually.

Florida Obstetrical and Gynecological Society. *President,* Charles J. Collins. *Secretary,* Dorothy D. Brame, Orlando, Fla. Next annual meeting, Belleair, April 10, 1949.

South Carolina Obstetrical and Gynecological Society. (1946) *President,* J. Decherd Guess. *Secretary,* Arthur L. Rivers, 231 Calhoun St., Charleston, S. C. Meetings held in spring and fall.

Buffalo Obstetrical and Gynecological Society. (1946) *President,* W. Herbert Burwig. *Secretary,* Clyde L. Randall, 925 Delaware Avenue, Buffalo, N. Y. Meetings held on the first Tuesday of October through May at the Saturn Club.

El Paso Gynecological Society. (1948) *President,* Gerald H. Jordan. *Secretary-Treasurer,* Gray E. Carpenter, 303 N. Oregon St., El Paso, Texas.

Kentucky Obstetrical and Gynecological Society. (1947) *President,* W. O. Johnson. *Secretary,* Edwin P. Solomon, 910 Heyburn Bldg., Louisville, Ky.

Indianapolis Obstetrical and Gynecological Society. (1947) *President,* David L. Smith. *Secretary,* Sprague H. Gardiner, 314 Hume Mansur Bldg., Indianapolis 4, Ind. Meetings held in January, April, and October.

Houston Obstetrical and Gynecological Society. (1939) *President,* John A. Wall. *Secretary-Treasurer,* Herman L. Gardner, Hermann Professional Bldg., Houston 5, Texas. Meetings held second Tuesday of each month except July, August, and September.

Iowa Obstetric and Gynecologic Society. *President,* J. H. Randall. *Secretary,* William C. Keettel, Iowa City, Iowa.